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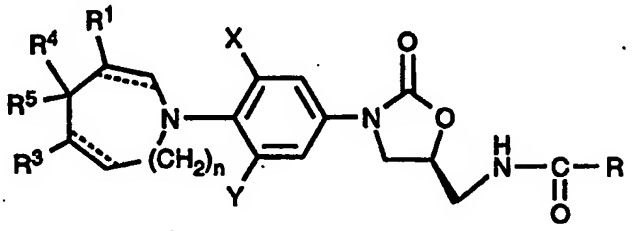
(54) Title: OXAZOLIDINONE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract

The present invention provides agents having high antimicrobial activity for preventing and treating infectious diseases. Thus, the present invention provides novel oxazolidinone derivatives represented by chemical formula (I), or pharmaceutically acceptable salts thereof, as well as antimicrobial compositions containing said derivatives or salts thereof as active ingredients.



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OXAZOLIDINONE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Field of Industrial Applicability

The present invention relates to novel oxazolidinone derivatives or pharmaceutically acceptable salts thereof, and pharmaceutical agents that contain them as active ingredients for preventing or treating infectious diseases.

More specifically, the present invention relates to useful antimicrobial agents effective against a number of human and veterinary pathogens, including multiply-resistant staphylococci and streptococci, as well as anaerobic organisms such as bacteroides and clostridia species, and acid-fast organisms such as Mycobacterium tuberculosis and Mycobacterium avium.

Information Disclosure

International Publication No. WO93/23384 discloses oxazolidinones containing a substituted diazine (piperazine) moiety and their uses as antimicrobials. International Publication No. WO93/09103 discloses substituted aryl and heteroaryl-phenyl-oxazolidinones useful as antimicrobials. International Publication No. WO90/02744 discloses 5'-indolinyl-5β-amidomethyloxazolidinones, 3-(fused-ring substituted)phenyl-5β-amidomethyloxazolidinones, and 3-(nitrogen substituted)-phenyl-5β-amidomethyloxazolidinones which are useful as antibacterial agents.

Other references disclosing various oxazolidinones include US Patent 4,801,600, J. Med. Chem., 32, 1673-81 (1989); J. Med. Chem., 33, 2569-78 (1990); Tetrahedron, 45, 1323-26 (1989); and J. Med. Chem., 35, 1156 (1992).

European Patent Publication 352,781 discloses phenyl and pyridyl substituted phenyl oxazolidinones. European Patent Publication 316,594 discloses 3-substituted styryl oxazolidinones. European Patent Publication 312,000 discloses phenylmethyl and pyridylmethyl substituted phenyl oxazolidinones.

Summary of the Invention

Problems to be Solved by the Invention

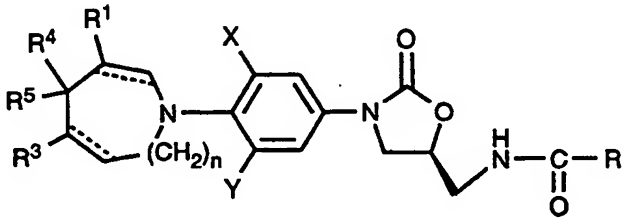
The object of the present invention is to provide novel oxazolidinone derivatives or pharmaceutically acceptable salts thereof which have high antimicrobial activities, and antimicrobial compositions that contain them as active ingredients.

Means for Solving the Problems

The present inventors conducted intensive studies in order to accomplish the above object. As a result, useful and novel oxazolidinone derivatives were found and

the present invention has been accomplished on the basis of the finding.

The present invention provides an oxazolidinone derivative represented by the general formula (I):



wherein

R is

(a) hydrogen atom,

(b) C_1-C_8 alkyl,

(c) C_3-C_6 cycloalkyl,

(d) amino,

(e) C_1-C_8 alkylamino,

(f) C_1-C_8 dialkylamino,

(g) C_1-C_8 alkoxy, or

(h) C_1-C_8 halogenoalkyl;

R^1 and R^3 are each and independently

(a) hydrogen atom,

(b) halogen atom,

(c) C_1-C_8 alkyl,

(d) C_3-C_6 cycloalkyl,

(e) $-(CH_2)_m-OR^{11}$, or

(f) $-C(=O)-R^{41}$;

X and Y are each and independently

(a) hydrogen atom, or

(b) halogen atom;

R^4 and R^5 are each and independently

(a) hydrogen atom,

(b) C_1-C_8 alkyl,

(c) C_1-C_8 alkoxy,

(d) C_1-C_8 alkylthio,

(e) $-(CH_2)_m-OR^{51}$,

(f) $-O-(CH_2)_m-OR^{51}$,

(g) $-NR^{42}R^{52}$,

(h) $-N=CH-NR^{44}R^{55}$,

(i) $-C(=O)-NR^{42}R^{52}$, or

(j) $-(CH_2)_m-C(=A)-R^{41}$,

or they may combine together to form

(k) =O,

(l) $=NR^{43}$,

(m) =S,

(n) $=CR^{44}R^{54}$, or

(o) an optionally substituted, unsaturated or saturated 5- or 6-membered hetero ring having 1-3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom;

R^{11} and R^{12} are each and independently

(a) hydrogen atom,

(b) C_1-C_8 alkyl, or

(c) methoxymethyl;

R^{41} is

(a) hydrogen atom,

(b) $-(CH_2)_m-OH$,

(c) C_1-C_8 alkyl,

(d) C_1-C_8 alkoxy,

(e) $-O-CH_2-O-C(=O)-R^{11}$, or

(f) $-(CH_2)_m-C(=O)-OR^{11}$;

R^{42} and R^{52} are each and independently

(a) hydrogen atom,

(b) $-(CH_2)_m-OR^{11}$,

(c) C_1-C_8 alkyl,

(d) $-C(=O)-R^{41}$,

(e) $-C(=O)-NR^{11}R^{12}$,

(f) $-(CH_2)_p$-phenyl,

(g) thiazol-2-yl,

or they may combine together to form a pyrrolidino group, a piperidino group, a piperazino group, a morpholino group, or a thiomorpholino group, each of which may be substituted by C_1-C_8 alkyl or $-(CH_2)_m-OH$;

R^{43} is

(a) hydrogen atom,

(b) $-OR^{51}$,

(c) C_1-C_8 alkyl,

(d) C_1-C_8 alkoxy,

(e) $-(CH_2)_p$-phenyl,

(f) $-NR^{42}R^{52}$,

(g) -NH-C(=NH)-NH_2,

(h) [1,2,4]triazol-4-yl, or

(i) cyano;

R^{44} and R^{54} are each and independently

(a) hydrogen atom,

(b) C_1-C_8 alkyl,

(c) $-C(=O)-R^{41}$, or

(d) $-(CH_2)_p$-phenyl;

R^{51} is

(a) hydrogen atom,

(b) C_1-C_8 alkyl,

(c) C_1-C_8 alkyl substituted by one or more hydroxy,

(d) C_2-C_8 alkenyl,

(e) C_1-C_8 halogenoalkyl,

(f) $-(CH_2)_m-OR^{11}$,

(g) $-(CH_2)_m-C(=O)-R^{41}$,

(h) $-C(=O)-(CH_2)_m-OR^{44}$, or

(i) tosyl;

A is

(a) oxygen atom, or

(b) ethyleneketal;

⎓ is a double bond or a simple bond;

m's are each and independently 0, 1 or 2;

n is 0 or 1;

p's are each and independently 1, 2, 3 or 4;

and C_1-C_8 alkyl, in each of the above definitions, may be each and independently substituted by one or more substituents selected from the group consisting of a halogen atom, a hydroxy group, C_1-C_8 alkoxy group, C_1-C_8 acyloxy group, an amino group, C_1-C_8 alkylamino group, C_1-C_8 dialkylamino group, -CN group and a carboxyl group,

or a pharmaceutically acceptable salt thereof.

The present invention also provides an antimicrobial agent that contains the oxazolidinone derivative or a pharmaceutically acceptable salt thereof as an effective ingredient. The antimicrobial agent containing the effective ingredient of the present invention can be used for treatment or prevention of infectious diseases. The term "treatment" as used herein means partial or total lessening of symptoms of a disease which a patient suffers from; the term "prevention" as used herein means partial or total avoidance of symptoms of a disease in a patient who, according to a doctor's diagnosis, may suffer from the disease or a related state unless the preventive measure is taken.

This invention provides novel oxazolidinone derivatives useful as preventatives and therapeutics for infectious diseases. The compounds of this invention have excellent antimicrobial action against various human and veterinary pathogens, including multiply-resistant staphylococci and streptococci, as well as anaerobic organisms such as bacteroides and clostridia species, and acid-fast Mycobacterium tuberculosis and Mycobacterium avium.

The carbon content of various hydrocarbon containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_i-C_j defines the number of carbon atoms present from the integer "i" to the integer "j" inclusive. Thus, C_1-C_3 alkyl refers to alkyl of 1-3 carbon atoms, inclusive, or methyl, ethyl, propyl, and isopropyl; C_1-C_8 alkyl is methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and isomeric forms thereof.

C_1-C_8 alkyl in the general formula (I) for the compounds of the present invention refers to methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and isomeric forms thereof; it means preferably methyl, ethyl, propyl, butyl, pentyl, hexyl and isomeric forms thereof, and more preferably methyl, ethyl, propyl, butyl and isomeric forms thereof.

The C_1-C_8 alkyl group may optionally be substituted by one or more substituents selected from the group consisting of a halogen atom, a hydroxy group, C_1-C_8 alkoxy group, C_1-C_8 acyloxy group, an amino group, C_1-C_8 alkylamino group, C_1-C_8 dialkylamino group, -CN group and a carboxyl group. Such substituted C_1-C_8 alkyl groups include 1-chloropropyl, 1-fuluoropropyl, 3-chloropropyl, 3-fuluoropropyl, hydroxymethyl, 3-hydroxypropyl, 2,3-dihydroxypropyl, 1-hydroxybutyl, 2-hydroxybutyl, 1-methoxypropyl, 1-octyloxypropyl, 1-acetoxypropyl, 1-aminopropyl, 1-aminooctyl, 1-butylaminopropyl, 1,1-dibutylaminopropyl, 1-cyanobutyl, 1-carboxybutyl and the like.

The term C_2-C_8 alkenyl means vinyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl, 1-hexenyl, 1-heptenyl, 1-octenyl and isomeric forms thereof, preferably an alkenyl group having 2 to 6 carbon atoms, and more preferably an alkenyl group having 2 to 4 carbon atoms.

The term C_3-C_6 cycloalkyl means cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The term C_1-C_8 alkylamino means an amino moiety containing one alkyl moiety having 1 to 8 carbon atoms, and the term C_1-C_8 dialkylamino means an amino moiety containing two alkyl moieties having 1 to 8 carbon atoms. For example, the two terms cover propylamino and dipropylamino, respectively; they mean preferably alkylamino and dialkylamino containing an alkyl moiety having 1 to 6 carbon atoms, and more preferably, alkylamino and dialkylamino containing an alkyl moiety having 1 to 4 carbon atoms.

The term C_1-C_8 alkoxy means methoxy, ethoxy, propoxy, butoxy, pentoxy, hexyloxy, heptyloxy, octyloxy and isomeric forms thereof, preferably an alkoxy group having 1 to 6 carbon atoms, and more preferably an alkoxy group having 1 to 4 carbon atoms. C_1-C_8 alkylthio means methythio, ethylthio, propylthio, butylthio, pentylthio, hexylthio, heptylthio, octylthio and isomeric forms thereof, preferably an alkylthio group having 1 to 6 carbon atoms, and more preferably an alkylthio group having 1 to 4 carbon atoms.

The halogen atom means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom. Preferred halogen atom for X and Y is a fluorine atom.

The term C_1-C_8 halogenoalkyl means a C_1-C_8 alkyl group in which the hydrogen atoms are substituted by the halogen atom defined above; this is preferably a halogen substituted alkyl group having 1-6 carbon atoms, more preferably 1-4 carbon atoms. C_1-C_8 halogenoalkyl may be exemplified by fluoromethyl, trifluoromethyl, 2-fluoroethyl, 2-chloroethyl, 2,2,2-trifluoroethyl and 2,3-difluoropropyl.

The unsaturated or saturated 5- or 6-membered ring that is to be formed by R^4 and R^5 when taken together and which have 1-3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom may be exemplified by hetero rings such as [1,3]dioxane, [1,3]dioxolane (ethyleneketal), imidazolidine, [1,3]dithiolane, [1,3]oxathiolane, oxazolidine and 2,3-dihydrothiazole. The hetero ring may optionally be substituted by C_1-C_4 alkyl or acetyl which may optionally be substituted by one or more hydroxy groups, and each of said substituent hydroxy group may optionally be substituted by C_1-C_4 alkyl,

methoxymethyl, ester and the like. The nitrogen atom forming the hetero rings may have a protective group such as an acetyl or hydroxyacetyl group. A preferred hetero ring within the definition is [1,3]dioxolane (ethyleneketal).

Where two variables are stated to be "each and independently" certain moieties, it is meant that each occurrence of each variable may be the same or different and will be selected from the moieties listed.

The term $-(CH_2)_p$-phenyl means preferably a benzyl group where p is 1.

The compounds of the present invention can be converted to their salts according to conventional methods.

Pharmaceutically acceptable salts means acid addition salts useful for administering the compounds of this invention and these include hydrochloride, hydrobromide, sulfate, phosphate, acetate, propionate, lactate, mesylate, maleate, succinate, tartrate, citrate, 2-hydroxyethyl sulfonate, fumarate and the like when a basic group is present. These salts may be in hydrated form. Some of the compounds of this invention may form metal salts such as sodium, potassium, calcium and magnesium salts and these are embraced by the term "pharmaceutically acceptable salts".

The preferred absolute configuration at C-5 of the oxazolidinone ring of compounds claimed in this invention is as represented in the structure of Formula (I). This absolute configuration is called (S) under the Cahn-Ingold-Prelog nomenclature system. It is this (S)-enantiomer which is pharmacologically active. The racemic mixture is useful in the same way and for the same purpose as the pure (S)-enantiomer; the difference is that twice as much racemic material must be used to produce the same antibacterial effect. Depending on substituents, the compounds of this invention may exist in geometric, optical and other isomeric forms and this invention embraces any of these isomers.

Particular preferred examples of the oxazolidinone derivatives represented by the general formula (I) are as follows (prefixed by compound numbers):

1) (S)-1-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperidine-4-carboxylic acid ethyl ester,

2) (S)-N-[3-(3-fluoro-4-piperidin-1-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

3) (S)-N-{3-[3-fluoro-4-(4-hydroxy-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

4) (S)-N-{3-[3-fluoro-4-(4-hydroxymethyl-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

5) (S)-N-{3-[4-(4-dibenzylamino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

6) (S)-N-{3-[4-(4-amino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

7) (S)-N-{3-[3-fluoro-4-(4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

8) (S)-1-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperidine-4-carboxylic acid,

9) (S)-N-{3-[4-(4-acetylamino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

10) (S)-N-(1-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperidin-4-yl)-2-hydroxy-acetamide,

11) (S)-N-{3-[3-fluoro-4-(4-hydroxyimino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

12) (S)-N-(3-{3-fluoro-4-[4-(2-oxo-propylidene)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

13) (S)-N-{3-[4-(4-acetyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

14) (S)-N-(3-{3-fluoro-4-[4-(2-hydroxy-acetyl)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

15) (S)-N-{3-[3-fluoro-4-(4-oxo-azepan-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

16) (S)-N-{3-[3-fluoro-4-(4-thioxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

17) (S)-N-{3-[3,5-difluoro-4-(4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

18) (S)-N-{3-[3-fluoro-4-(3-fluoro-4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

19) (S)-N-{3-[3-fluoro-4-(3-methyl-4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

20) (S)-N-{3-[3-fluoro-4-(3-hydroxymethyl-5-methyl-4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

21) (S)-N-{3-[3-fluoro-4-(4-methyl-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

22) (S)-N-{3-[3-fluoro-4-(4-methoxy-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

23) (S)-N-{3-[3-fluoro-4-(4-methylsulfanyl-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

24) (S)-N-{3-[4-(4-dimethylamino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

25) (S)-1-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperidine-4-carboxylic acid amide,

26) (S)-N-{3-[3-fluoro-4-(4-hydroxymethylimino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

27) (S)-N-{3-[3-fluoro-4-(4-methylimino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

28) (S)-N-{3-[3-fluoro-4-(3-hydroxy-4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide.

29) (S)-N-{3-[3-fluoro-4-(4-methoxymethoxy-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

30) (S)-N-{3-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

31) (S)-N-{3-[3-fluoro-4-(4-methoxyimino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

32) (S)-N-{3-[3-fluoro-4-(4-methoxycarbonylamino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

33) (S)-N-{3-[3-fluoro-4-(4-methoxycarbonylhydrazono-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

34) (S)-N-(3-{3-fluoro-4-[4-(2-methyl-[1,3]dioxolan-2-ylmethyl)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

35) (S)-N-(3-{3-fluoro-4-[4-(2-oxo-propyl)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

36) (S)-8-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-1,4-dioxa-8-aza-spiro[4.5]decane-6-carboxylic acid methyl ester,

37) (S)-1-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-4-oxo-piperidin-3-carboxylic acid methyl ester,

38) (S)-N-{3-[3-fluoro-4-(4-oxo-4H-pyridin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

39) (S)-N-(3-{3-fluoro-4-[4-(2-methyl-[1,3]dioxolan-2-yl)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

40) (S)-N-{3-[4-(4-acetyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

41) (S)-N-{3-[3-fluoro-4-(3-hydroxymethyl-4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

42) (S)-N-{3-[3-fluoro-4-(4-methoxycarbonyloxyimino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

43) (S)-N-{3-[3-fluoro-4-(4-semicarbazono-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

44) (S)-N-(3-{3-fluoro-4-[4-(morpholin-4-ylimino)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

45) (S)-N-[3-(3-fluoro-4-{4-[(2-hydroxy-ethyl)-hydrazono]-piperidin-1-yl}-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

46) (S)-N-{3-[3-fluoro-4-(4-amidinohydrazono-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

47) (S)-N-{3-[3-fluoro-4-(4-acetoxyacetoxyimino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

48) (S)-N-(3-{3-fluoro-4-[4-(2-hydroxymethyl-[1,3]dioxolan-2-yl)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

49) (S)-N-{3-[3-fluoro-4-(4-benzyloxyacetoxyimino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

50) (S)-N-{3-[3-fluoro-4-(4-hydrazono-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

51) (S)-(1-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperidin-4-ylideneaminooxy)-acetic acid methyl ester,

52) (S)-N-(3-{3-fluoro-4-[4-(2-hydroxy-ethoxyimino)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

53) (S)-N-[3-(3-fluoro-4-{4-[4-(2-hydroxy-ethyl)-piperazin-1-ylimino]-piperidin-1-yl}-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

54) (S)-N-[3-(3-fluoro-4-{4-[(2-hydroxy-acetyl)-hydrazono]-piperidin-1-yl}-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

55) (S)-N-(3-{3-fluoro-4-[4-([1,2,4]triazol-4-ylimino)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

56) (S)-N-{3-[3-fluoro-4-(2-hydroxymethyl-1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

57) (S)-N-(3-{3-fluoro-4-[4-(2-methoxymethoxy-ethoxyimino)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

58) (S)-N-(3-{3-fluoro-4-[4-(2-hydroxy-acetyl)-1-oxa-4,8-diaza-spiro[4.5]dec-8-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

59) (S)-N-{3-[4-(4-cyanoimino-piperidin-1-yl)-3-fluoro-phenyl)-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

60) (S)-(1-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperidin-4-ylidenehydrazinocarbonyl)-acetic acid ethyl ester,

61) (S)-N-(3-{3-fluoro-4-[2-(methoxymethoxy-methyl)-1,4-dioxa-8-aza-spiro[4.5]dec-8-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

62) (S)-N-{3-[4-(4-allyloxyimino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

63) (S)-N-{3-[3-fluoro-4-(4-methoxyamino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

64) (S)-N-{3-[3-fluoro-4-(4-methoxymethoxyimino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

65) toluene-4-sulfonic acid (S)-1-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperidin-4-yl ester,

66) (S)-N-(3-{4-[4-(2,3-dihydroxy-propoxyimino)-piperidin-1-yl]-3-fluoro-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

67) (S)-N-(3-{3-fluoro-4-[4-(thiazol-2-ylamino)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

68) (S)-N-(3-{3-fluoro-4-[4-(2-methoxy-ethylamino)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

69) (S)-N-(3-{4-[4-(acetoxy-methoxy-carbonylamino)-piperidin-1-yl]-3-fluoro-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

70) (S)-N-{3-[3-fluoro-4-(4-methylamino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

71) (S)-N-{3-[4-(4-dimethylamino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

72) (S)-N-{3-[4-(4-dimethylaminomethyleneamino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

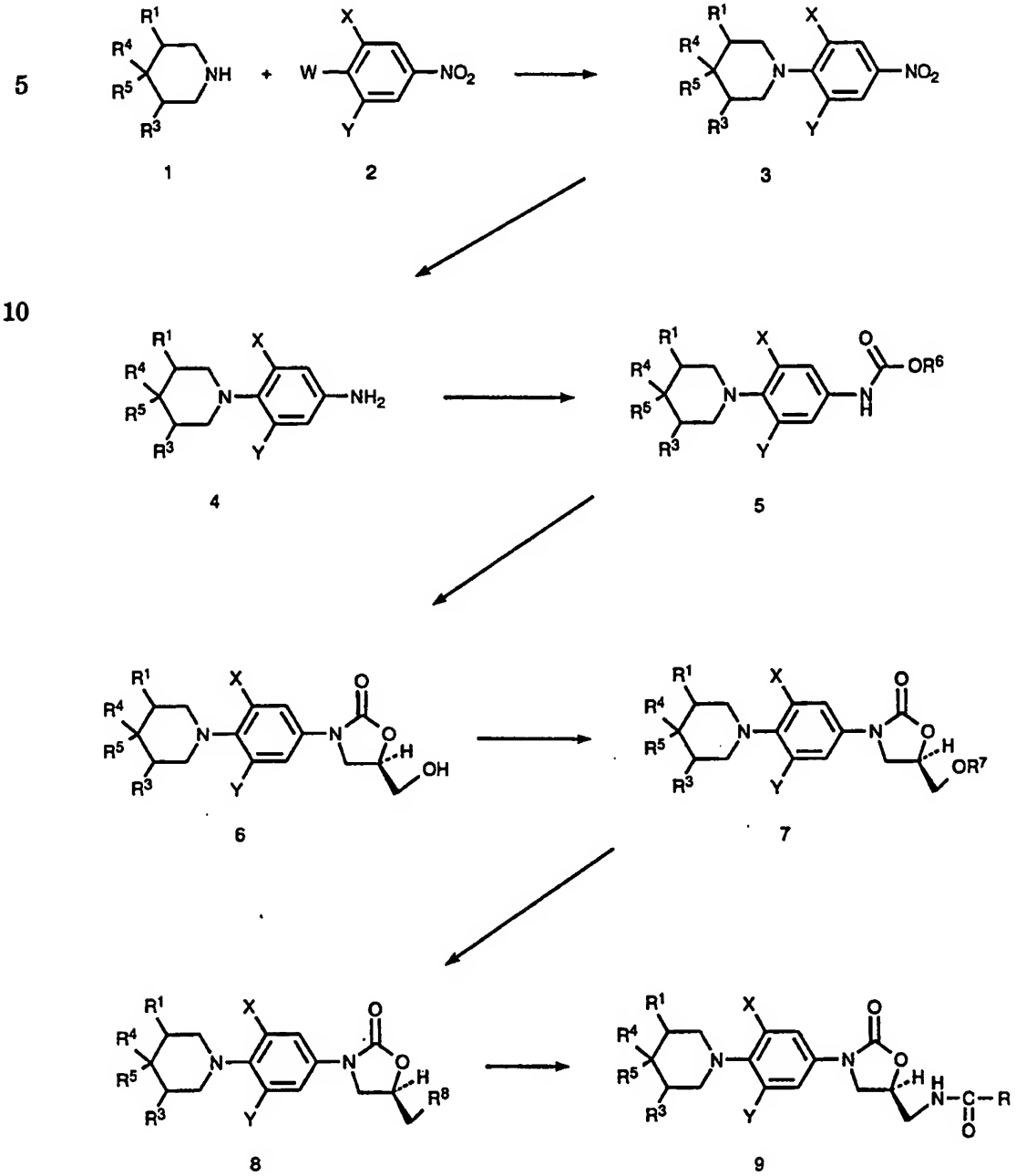
73) (S)-2-fluoro-N-{3-[3-fluoro-4-(4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide and

74) (S)-N-{3-[3-fluoro-4-(4-morpholin-4-yl-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide.

The compounds represented by the general formula (I) can be prepared by the method of reaction scheme 1. The method of synthesis is described below as regards substituted piperidines which are compounds of the general formula (I) where n = 0. It should however be noted that substituted azepans where n = 1 can also be

synthesized by similar methods.

SCHEME 1



As shown, substituted piperidine of structure 1 or 4-hydroxypyridine is reacted with nitrobenzene 2 (Y = halogen or trifluoromethanesulfonate) in the presence of a suitable base such as N,N-diisopropylethylamine, sodium hydride or disodium hydrogenphosphate, and in a suitable solvent such as acetonitrile, tetrahydrofuran (THF), ethyl acetate, dimethyl sulfoxide (DMSO) or dimethyl formamide (DMF) at room temperature or reflux temperature to provide the adduct 3. When necessary, the side chains of R^1, R^3, R^4 and R^5 may be protected with a suitable protecting group(s) such as a benzyl or others that are described in Greene, T.W.; Wuts, P.G.M. "Protective Groups in Organic Synthesis", 2nd ed.,; John Wiley & Sons: New York (1991), the protecting groups being optionally removed after the synthesis. The nitro group of structure 3 is then reduced by hydrogenation in the presence of a suitable catalyst such as palladium on carbon or Lindlar catalyst in a suitable solvent such as ethyl acetate, THF, methanol, methylene chloride, chloroform or a mixture thereof (hydrogen is supplied in the form of a gas or indirectly via ammonium formate). The aniline 4 is then converted to its benzyl (R^6 = CH_2Ph) or methyl (R^6 = CH_3) urethane derivative 5, employing standard Schotten-Baumann conditions or other means known to one skilled in the art. The urethane 5 is then deprotonated by the action of a suitable base such as n-butyllithium or lithium bis(trimethylsilyl)amide in a suitable solvent such as THF or DMF at a suitable temperature in the range -78 to -40°C to give a lithiated intermediate which is then treated with commercially available (-)-(R)-glycidyl butyrate. Warming to ambient temperature affords the compound 6 which is the enantiomer of hydroxymethyl-substituted oxazolidinone. Compound 6 is then converted to the corresponding mesylate (R^7 = methanesulfonyl) or aryl sulfonate (R^7 = $ArSO_2$, for example p-toluenesulfonyl) by reaction with, for example, methanesulfonyl chloride/pyridine or methanesulfonyl chloride/triethyl-amine/dichloromethane or methanesulfonyl chloride/triethylamine/DMSO or p-toluenesulfonyl chloride/pyridine. The resultant sulfonate derivative 7 is then reacted with sodium azide or potassium azide or the like in a solvent such as DMF or 1-methyl-2-pyrrolidinone optionally in the presence of a catalyst such as 18-crown-6 at a temperature of 50-90°C to afford the azide 8 (R^8 = N_3). The azide is then reduced by hydrogenation with palladium on carbon, Lindlar catalyst or a platinum catalyst in an appropriate solvent such as ethyl acetate, methanol, methylene chloride, chloroform or a mixture thereof to give the corresponding amine 8 (R^8 = NH_2). Alternatively, the azide can be reduced by reaction with a trivalent phosphorus compound such as triphenylphosphine in a suitable solvent such as THF

followed by the addition of water. Alternatively, the mesylate or aryl sulfonate can be displaced with potassium phthalimide by refluxing in acetonitrile or other suitable solvent. The phthalimide 8 (R^8 = phthalimide) is then deprotected by the addition of aqueous methyl amine in refluxing ethanol, to give the amine 8 (R^8 = NH_2). The amine 8 is then acylated by methods known to those skilled in the art to give oxazolidinones of structure 9. For example, the amine can be reacted with an acid chloride or anhydride in a basic solvent such as pyridine at a temperature ranging from -30 to 30°C to provide the acylated compound 9 (R = optionally substituted alkyl). A substituent such as amino, hydroxy, ester or carbonyl group in R^4 or R^5 can be converted to the corresponding derivative such as alkylamide, ether, carboxyl, hydroxyalkyl or oxime group by methods known to those skilled in the art. It will be apparent to one skilled in the art that other acyl groups within the scope of this invention can be readily appended to the amine 8 (R^6 = NH_2) by standard acylation techniques, for example, those highlighted in March, J. "Advanced Organic Chemistry", 3rd ed.; John Wiley & Sons: New York, 1985; p 370-375, to give additional examples of compound 9. Any appended protecting group on the side chains of R^1, R^3, R^4 and R^5 on the piperidine ring can be removed employing appropriate conditions such as those noted in Greene, T.W.; Wuts, P.G.M., "Protective Groups in Organic Synthesis," 2nd ed.; John Wiley & Sons: New York (1991). The compounds of structure 9 represent examples of piperidine-substituted oxazolidinone antimicrobial agents of Formula (I), which are the subject of this invention.

These compounds are useful for the treatment of microbial infections in humans and other warm blooded animals by either parenteral, oral, or topical administration.

The pharmaceutical compositions of this invention may be prepared by combining the compounds of Formula (I) of this invention with a solid or liquid pharmaceutically acceptable carrier and, optionally, with pharmaceutically acceptable adjuvants and excipients employing standard and conventional techniques. Solid form compositions include powders, tablets, dispersible granules, capsules and suppositories. A solid carrier can be at least one substance which may also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Inert solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, cellulosic materials, low melting wax, cocoa butter, and the like. Liquid form compositions include solutions, suspensions and emulsions. For

example, there may be provided solutions of the compounds of this invention dissolved in water and water-propylene glycol and water-polyethylene glycol systems, optionally containing conventional coloring agents, flavoring agents, stabilizers and thickening agents.

Preferably, the pharmaceutical composition is provided employing conventional techniques in unit dosage form containing effective or appropriate amounts of the active component, that is, the compound of Formula (I) according to this invention.

The quantity of active component, that is the compound of Formula (I) according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application method, the potency of the particular compound and the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

In therapeutic use for treating, or combatting bacterial infections in humans and other animals that have been diagnosed with bacterial infections, the compounds or pharmaceutical compositions thereof will be administered orally, parenterally and/or topically at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which will be antibacterially effective. Generally, such antibacterially effective amount of dosage of active component will be in the range of about 0.1 to about 100 mg/kg, more preferably about 3.0 to about 50 mg/kg of body weight/day. It is to be understood that the dosages may vary depending upon the requirements of the patient, the severity of the bacterial infection being treated, and the particular compound being used. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g., two to four times per day.

The compounds of Formula (I) according to this invention are administered parenterally, i.e., by injection, for example, by intravenous injection or by other parenteral routes of administration. Pharmaceutical compositions for parenteral administration will generally contain a pharmaceutically acceptable amount of the compound according to Formula (I) as a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as, for example,

water-for-injection and a suitably buffered isotonic solution, for example, having a pH of about 3.5-6. Suitable buffering agents include, for example, trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine, to name a few. The compound according to Formula (I) generally will be dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 mg/ml to about 400 mg/ml. The resulting liquid pharmaceutical composition will be administered so as to obtain the above-mentioned antibacterially effective amount of dosage. The compounds of Formula (I) according to this invention are advantageously administered orally in solid and liquid dosage forms.

As a topical treatment, an effective amount of Formula (I) is admixed in a pharmaceutically acceptable gel or cream vehicle that can be applied to the patient's skin at the area of treatment. Preparation of such creams and gels is well known in the art and can include penetration enhancers.

The compounds of this invention are useful antimicrobial agents, effective against various human and veterinary pathogens, including multiply-resistant staphylococci and streptococci, as well as anaerobic organisms such as bacteroides and clostridia species, and acid-resistant organisms such as Mycobacterium tuberculosis and Mycobacterium avium.

We now describe the test method for verifying the antimicrobial action of compounds within the scope of this invention. Compounds of this invention were subjected to various antimicrobial activity tests, in which they exhibited antimicrobial activity against multiply-resistant staphylococci and streptococci, as well as anaerobic organisms such as bacteroides and clostridia species, and acid-resistant organisms such as Mycobacterium tuberculosis and Mycobacterium avium. MIC (minimum inhibitory concentration) data for compounds of this invention against typical organisms were determined by the MIC test method to be described below and the results are shown in Table 1. The antimicrobial action of compounds of this invention was also verified by the Murine Assay procedure (in vivo) to be described below. Compounds with numbers 7, 11, 30 and 31 had ED_{50} values of 8.1 mg/kg, 8.2 mg/kg, 2.8 mg/kg and 5.0 mg/kg, respectively, upon oral administration; hence, they were as effective as the control Vancomycin.

MIC Test Method

The in vitro MICs of test compounds were determined by a standard agar dilution method. A stock drug solution of each analog is prepared in the preferred solvent, usually DMSO:H_2O (1:3). Serial 2-fold dilutions of each sample are made

using 1.0 ml aliquots of sterile distilled water. To each 1.0 ml aliquot of drug is added 9 ml of molten Mueller Hinton agar medium. The drug-supplemented agar is mixed, poured into 15 x 100 mm petri dishes, and allowed to solidify and dry prior to inoculation.

Vials of each of the test organisms are maintained frozen in the vapor phase of a liquid nitrogen freezer. Test cultures are grown overnight at 35°C on the medium appropriate for the organism. Colonies are harvested with a sterile swab, and cell suspensions are prepared in Trypticase Soy broth (TSB) to equal the turbidity of a 0.5 McFarland standard. A 1:20 dilution of each suspension is made in TSB. The plates containing the drug supplemented agar are inoculated with a 0.001 ml drop of the cell suspension using a Steers replicator, yielding approximately 10^4 to 10^5 cells per spot. The plates are incubated overnight at 35°C.

Following incubation the Minimum Inhibitory Concentration (MIC µg/ml), the lowest concentration of drug that inhibits visible growth of the organism, is read and recorded. Vancomycin is included in the assay and serves as a comparator and quality control compound. The result for the control compound against each test strain is compared to previous and/or published MIC results as a means of validating the test.

Table 1

Minimum Inhibitory Concentrations

(MIC, μg/ml)

Compound No.	S. aureus	S. epidermidis	S. pyogenes	M. tuberculosis
1	8*	2	2	1
2	8*	1	4	-
3	8	2	2	1
4	8	2	2	-
6	>64	32	1	-
7	2	0.5	2	-
9	16	2	4	-
10	16	2	2	-
11	2	1	1	-
29	8	2	8	-
30	8	2	4	-
31	4	1	4	-
32	4	2	2	-
33	2	0.5	1	-
34	16	4	4	-
35	8	2	2	-
36	16	4	4	-
37	16	4	4	-
38	16	2	0.5	-
39	8	2	2	-
40	4	1	2	-

	41	8	2	2	-
	42	2	0.5	1	-
	43	2	0.5	2	-
	44	4	0.5	2	-
5	45	4	0.5	1	-
	46	8	2	0.5	-
	47	4	0.5	1	-
	48	16	2	24	-
	49	2	0.5	2	-
10	50	2	0.5	2	-
	51	8	1	2	-
	52	8	1	2	-
	53	4	0.5	1	-
	54	16	4	4	-
15	55	4	1	2	-
	56	16	2	4	-
	57	16	2	4	-
	58	16	4	4	-
	60	4	1	2	-
20	61	16	4	8	-
	62	8	1	2	-
	63	4	2	4	-
	64	8	2	2	-
	65	8	4	8	-
25	66	8	1	2	-
	67	16	2	2	-

68	32	2	1	-
69	8	1	0.5	-
71	32	2	1	-
Vanco-mycin	1	2	0.5	-

S. aureus: Staphylococcus aureus (UC 9213, *: UC 9218)
S. epidermidis: Staphylococcus epidermidis (UC 12084)
S. pyogenos: Streptococcus pyogenes (UC 152)
M. tuberculosis: Mycobacterium tuberculosis

Murine Assay Procedure

Groups of female mice (six mice of 18-20 grams each) were injected intraperitoneally with Staphylococcus aureus (UC 9213) bacteria which were thawed just prior to use and suspended in brain heart infusion with 4% brewer's yeast (Staphylococcus aureus) or brain heart infusion (Streptococcus species). Antibiotic treatment at six dose levels per drug (compound) was administered one hour and five hours after infection by either oral intubation or subcutaneous routes. Survival was observed daily for six days. ED_{50} values based on mortality ratios were calculated using probit analysis. The subject compounds were compared against vancomycin as a control.

It should be noted here that none of the compounds of this invention, nor pharmaceutically acceptable salts thereof have been found to have toxicity that would cause any problem.

Description of the Preferred Embodiments

The following examples are provided to further illustrate this invention but they should not be taken as limiting.

Example 1

Preparation of (S)-N-[3-(3-fluoro-4-piperidin-1-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl)-acetamide (Compound No. 2):

Diisopropylethylamine (15.7 ml) and 3,4-difluoronitrobenzene (5.0 ml) were added successively to an ethyl acetate solution (70 ml) of piperidine (5.77 g) and the mixture was stirred at room temperature for 2 days. Water was added to the reaction solution and the separating ethyl acetate layer was washed with water and brine, dried over anhydrous sodium sulfate. The solvent was evaporated to afford a

nitro compound (10.1 g) in a yield of 100%. Palladium on carbon (10%, 1.0 g) was added to an ethyl acetate solution (101 ml) of the nitro compound (10.1 g) and the mixture was stirred at room temperature for 14 h under hydrogen atmosphere. The palladium on carbon was filtered off and the filtrate was concentrated under vacuum to yield an amine (8.75 g, 100%). Sodium hydrogencarbonate (5.0 g) and benzyloxycarbonyl chloride (8.4 ml) were added successively to a tetrahydrofuran (THF) solution (100 ml) of the amine (8.75 g), and the mixture was stirred at room temperature for 14 h. Water was added to the reaction solution and the separating THF layer was washed with water and brine, dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by silica gel column chromatography (solvent: ethyl acetate/hexane/chloroform = 1/6/4) to afford a benzyl carbamate (14.5 g) in a yield of 98%. Butyl lithium (1.6 M hexane solution: 5.2 ml) was added to a THF solution (24 ml) of the benzyl carbamate (2.75 g) at -78°C and the mixture was stirred for 5 min. At the same temperature, (R)-(-)-glycidyl butyrate (1.25 ml) was added to the stirred solution and the mixture was stirred for 14 h while the temperature was raised slowly to room temperature. Water was added to the reaction solution and the separating THF layer was washed with water and brine, dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by silica gel column chromatography (solvent: ethyl acetate/hexane = 3/1) to afford an alcohol (2.20 g) in a yield of 89%. Tosyl chloride (2.85 g) was added to a pyridine solution (8 ml) of the alcohol (2.20 g) and the mixture was stirred at room temperature for 6 h. Water (32 ml) was added to the reaction solution and the mixture was stirred for 1 h. The resulting precipitate was collected by filtration and washed with water, followed by drying under vacuum at room temperature to afford a tosylate (3.28 g) in a yield of 98%. Sodium azide (3.80 g) was added to a dimethylformamide (DMF) solution (23 ml) of the tosylate (3.28 g) at room temperature and the mixture was stirred at 65°C for 5.5 h. After the reaction mixture was cooled to room temperature, water was added and the mixture was extracted with ethyl acetate; the organic layer was concentrated under vacuum. The resulting residue was dissolved in ethyl acetate and washed with water and brine, dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by silica gel column chromatography (solvent: ethyl acetate/hexane = 1/1) to afford an azide (2.20 g) in a yield of 94%. Acetic anhydride (0.65 ml) and pyridine (1.0 ml) were added to an ethyl acetate solution (19 ml) of the azide (2.20 g) at room temperature; after addition of palladium on carbon (10%, 0.22 g), the mixture was stirred at room temperature for 6 h under 1 atm hydrogen

atmosphere. The palladium on carbon was filtered off and the filtrate was washed with water and brine, dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by silica gel column chromatography (solvent: acetone/hexane = 1/1) to afford the title compound (1.47 g) in a yield of 64%.

Example 2

Preparation of (S)-N-{3-[3-fluoro-4-(4-hydroxymethyl-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 4):

Using a commercially available piperidine-4-carboxylic acid ethyl ester, (S)-1-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperidine-4-carboxylic acid ethyl ester (Compound No. 1) was synthesized by the same method as in Example 1. To a THF solution (6.6 ml) of this compound (661 mg), lithium chloride (275 mg), sodium borohydride (245 mg) and ethanol (4.5 ml) were added successively and the mixture was stirred at room temperature for 14 h. A saturated aqueous ammonium chloride solution was added to the reaction solution and the reaction mixture was extracted with methylene chloride; the organic layer was washed with water and brine, dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by silica gel column chromatography (solvent: chloroform/methanol = 25/1 - 15/1) to afford the title compound (402 mg) in a yield of 68%.

Example 3

Preparation of (S)-N-{3-[3-fluoro-4-(4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 7):

Using a commercially available 1,4-dioxo-8-aza-spiro[4.5]decane, (S)-N-{3-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 30) was synthesized by the same method as in Example 1. To an acetone solution (70 ml) of this compound (3.79 g), water (20 ml) and p-toluenesulfonic acid monohydrate (3.66 g) were added successively and the mixture was heated under reflux for 3 h. After the reaction mixture was cooled to room temperature, acetone was distilled off and the aqueous layer was neutralized with triethylamine. The solution was extracted with methylene chloride and the organic layer was washed with brine, dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by silica gel column chromatography (solvent: chloroform/methanol = 50/1 - 25/1) to afford the title compound (3.05 g) in a yield of 91%.

Example 4

Preparation of (S)-N-{3-[4-(4-amino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 6):

Sodium carbonate (18.1 g) and benzyl bromide (10.0 ml) were added successively to an acetonitrile solution (80 ml) of (4-amino-piperidin-1-yl)-acetic acid ethyl ester (4.89 g) and the mixture was stirred at room temperature for 14 h. The reaction solution was filtered and the filtrate was concentrated under vacuum. The residue was dissolved in methylene chloride and washed with water and brine, dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by silica gel column chromatography (solvent: ethyl acetate/hexane = 1/6) to afford a dibenzyl compound (8.24 g) in a yield of 82%. Potassium hydroxide (34 g) was added to an ethylene glycol solution (170 ml) of the dibenzyl compound (8.24 g) and the mixture was stirred for 15 min. Thereafter, hydrazine monohydrate (5.7 ml) was added and the mixture was heated under reflux for 2 h. After the reaction mixture was cooled to room temperature, water was added to the reaction solution and the precipitating crystal was collected by filtration and washed with water, followed by drying under vacuum at room temperature to afford dibenzyl-piperidin-4-yl-amine (6.43 g) in a yield of 98%.

Using the amino compound, (S)-N-{3-[4-(4-dibenzylamino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 5) was synthesized by the same method as in Example 1. To a methanol solution (200 ml) of this compound (5.28 g), palladium hydroxide on carbon (20%, 3.3 g) was added and the mixture was stirred at room temperature under 3 atm hydrogen atmosphere. Palladium hydroxide on carbon was filtered off and the filtrate was concentrated under vacuum to afford the title compound (3.48 g) in a yield of 100%.

Example 5

Preparation of (S)-N-{3-[3-fluoro-4-(4-hydroxyimino- piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}- acetamide (Compound No. 11):

Sodium acetate (517 mg) and hydroxylamine hydrochloride (219 mg) were successively added to a methanol-methylene chloride solution (10-10 ml) of 1.00 g of the (S)-N-{3-[3-fluoro-4-(4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 7) synthesized in Example 3, and the mixture was stirred at room temperature for 2 days. The solvent was evaporated and the residue was dissolved in methanol, followed by addition of a silica gel (8 g). Methanol was evaporated and the residue was purified by silica gel column chromatography (solvent: chloroform/methanol = 50/1 - 25/1) to afford the title compound (852 mg) in a yield of 82%.

Example 6

Preparation of (S)-N-{3-[3-fluoro-4-(4-methoxycarbonylhydrazono-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 33):

Methyl carbazinate (135 mg) was added to a methanol- methylene chloride solution (5-4 ml) of 500 mg of the (S)-N-{3-[3-fluoro-4-(4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 7) synthesized in Example 3, and the mixture was stirred at room temperature for 14 h. The solvent was evaporated and the residue was purified by silica gel column chromatography (solvent: chloroform/methanol = 50/1) to afford the title compound (487 mg) in a yield of 81%.

Example 7

Preparation of (S)-N-(3-{3-fluoro-4-[4-(2-methyl-[1,3]dioxolan-2-ylmethyl)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide (Compound No. 34):

Dimethyl(2-oxopropyl)phosphate (2.85 ml) and N-benzyl-4-piperidone (3.00 g) were successively added to an ethanol solution (14 ml) of potassium hydroxide (0.93 g) and the mixture was stirred at room temperature for 14 h. Water was added to the reaction solution and the mixture was extracted with ether, washed with water and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by ODS-silica gel column chromatography (solvent: methanol/water = 2/1 - 4/1) to afford an enone (2.07 g) in a yield of 57%. To a benzene solution (50 ml) of the enone (3.69 g), ethylene glycol (4.49 ml) and p-toluenesulfonic acid monohydrate (3.37 g) were added successively and the mixture was refluxed for 5 h under heating with a Dean-Stark apparatus. After the reaction mixture was cooled to room temperature, a saturated aqueous sodium carbonate solution was added and the mixture was extracted with ethyl acetate, washed with water and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated to afford a ketal benzyl compound (4.20 g) in a yield of 95%. To a methanol solution (42 ml) of the ketal benzyl compound (4.20 g), palladium hydroxide on carbon (0.42 g) was added and the mixture was stirred for 2 days under 3 atm hydrogen atmosphere. The palladium hydroxide on carbon was filtered off and the filtrate was concentrated under vacuum to afford a ketal compound (2.80 g) in a yield of 98%. Using this compound, the procedure of Example 1 was repeated to afford the title compound.

Example 8

Preparation of (S)-8-{4-[5-acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-

phenyl}-1,4-dioxa-8-aza-spiro[4.5]decane-6-carboxylic acid methyl ester (Compound No. 36):

Diisopropylethylamine (7.71 ml), then benzyloxycarbonyl chloride (3.0 ml) were added to a dichloromethane solution (40 ml) of 3-carbomethoxy-4-piperidone hydrochloride (3.43 g) at 0°C and the mixture was stirred at room temperature for 14 h. The solvent was evaporated and the residue was purified by silica gel column chromatography (solvent: hexane/ethyl acetate = 7/3) to afford an N-benzyl carbamate (4.57 g) in a yield of 79%. The benzyl carbamate, p-toluenesulfonic acid hydrate (2.45 g) and ethylene glycol (8.69 g) were added to benzene (100 ml) and the mixture was refluxed for 6 h under heating with water being removed continuously with a water separator. After being cooled to room temperature, the reaction solution was washed first with a saturated aqueous sodium hydrogencarbonate, then with water; the organic layer was dried and concentrated under vacuum to afford an ethyleneketal benzyl carbamate (4.89 g) in a yield of 94%. This compound was dissolved in a mixed solvent consisting of dichloromethane (20 ml) and methanol (50 ml). To the solution, palladium hydroxide on carbon (20%, 500 mg) was added and the mixture was stirred at room temperature for 14 h under 3 atm hydrogen atmosphere. The palladium hydroxide on carbon was filtered off and the filtrate was concentrated under vacuum to afford an ethyleneketal compound (3.44 g) in a yield of 100%. Using this compound, the procedure of Example 1 was repeated to afford the title compound.

Example 9

Preparation of (S)-1-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-4-oxo-piperidin-3-carboxylic acid methyl ester (Compound No. 37):

Using 400 mg of the (S)-8-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-1,4-dioxa-8-aza-spiro[4.5]decane-6-carboxylic acid methyl ester (Compound No. 36) synthesized in Example 8, the procedure of Example 3 was repeated to afford the title compound (49 mg).

Example 10

Preparation of (S)-N-{3-[3-fluoro-4-(4-oxo-4H-pyridin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 38):

Sodium hydride (1.88 g) was added to an anhydrous dimethylformamide (DMF) solution (50 ml) of 4-hydroxypyridine (3.28 g) at 0°C and the mixture was stirred for 30 min. Subsequently, 3,4-difluoronitrobenzene (5.0 g) was added at the same temperature and the mixture was stirred at room temperature for 14 h. Water was added to the reaction solution and the solvent was evaporated. Toluene was

added and water was removed by azeotropy and the residue was suspended in dichloromethane (100 ml). The insolubles were rejected by filtration through Celite and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (solvent: methanol/dichloromethane = 5/95) to afford a nitro compound (4.89 g) in a yield of 66%. The nitro compound was reduced catalytically with a Lindlar catalyst and subsequently treated with benzyloxycarbonyl chloride to afford a benzyl carbamate (1.71 g) in a yield of 24%. Lithium bis(trimethylsilyl)amide (1M THF solution; 4.0 ml) was added to a DMF solution (20 ml) of the benzyl carbamate (1.22 g) at -78°C and the mixture was stirred for 5 min. At the same temperature, (R)-(-)-glycidyl butyrate (0.56 ml) was added to the stirred solution and the mixture was stirred for 14 h while the temperature was raised slowly to room temperature, with the stirring being continued for three more days at room temperature. Water was added to the reaction solution and the solvent was evaporated. A dichloromethane-soluble portion was produced by dehydration and desalting in accordance with the same procedure as described above and purified by silica gel column chromatography (solvent: methanol/dichloromethane = 7/93) to afford an alcohol (745 mg). Triethylamine (0.4 ml), then methanesulfonyl chloride (0.2 ml) were added to a dimethyl sulfoxide solution (10 ml) of the alcohol (540 mg) at 0°C and the mixture was stirred at room temperature for 18 h. The solvent was evaporated and the residue was dissolved in DMF (10 ml). Sodium azide (160 ml) was added to the solution at room temperature and the mixture was stirred at 65°C for 14 h. After the reaction mixture was cooled to room temperature, the insolubles were filtered off and the filtrate was concentrated under vacuum. The resulting residue was purified by silica gel column chromatography (solvent: methanol/dichloromethane = 5/95) to afford an azide (149 mg) in a yield of 26%. Triphenylphosphine (137 mg) was added to an anhydrous TFH solution (4 ml) of the azide at room temperature and the mixture was stirred for 2 h. Water (0.1 ml) was added to the reaction mixture, followed by stirring at 40°C for 4 h, then at room temperature for 14 h. The solvent was evaporated and the residue was dehydrated by azeotropy with toluene. The resulting residue was suspended in dichloromethane (10 ml) and, after addition of pyridine (0.8 ml) and acetic anhydride (1.0 ml) at 0°C, the mixture was stirred at room temperature for 6 h. The solvent was evaporated and the residue was purified by silica gel column chromatography (solvent: methanol/dichloromethane = 7/93) to afford the title compound (167 mg) in a yield of 100%.

Example 11

Preparation of (S)-N-(3-{3-fluoro-4-[4-(2-methyl-[1,3]dioxolan-2-yl)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide (Compound No. 39):

Potassium carbonate (5.27 g) and benzyl bromide (3.97 ml) were successively added to an acetonitrile solution (80 ml) of ethyl isonipecotate (5.00 g) and the mixture was stirred at room temperature for 14 h.

Water was added to the reaction solution and the mixture was extracted with ethyl acetate, washed with water and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by silica gel column chromatography (solvent: ethyl acetate/hexane = 1/2) to afford a benzyl compound (7.03 g) in a yield of 89%. A THF solution (25 ml) of the benzyl compound (5.00 g) was added dropwise to a THF solution (10 ml) of lithium diisopropylamide (1.5 M cyclohexane solution; 17.5 ml) at -78°C and the mixture was stirred for 15 min. At the same temperature, a THF solution (20 ml) of acetyl chloride (2.16 ml) was added dropwise and the mixture was stirred at -78°C for 30 min and then for 14 h with the temperature raised to room temperature. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution and the mixture was extracted with ethyl acetate, washed with water and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by silica gel column chromatography (solvent: ethyl acetate/hexane = 1/2) to afford a crude acetyl-ester compound (5.05 g). A 10% aqueous sodium hydroxide solution (20 ml) was added to a THF solution (20 ml) of the crude acetyl-ester compound (5.05 g) and the mixture was stirred at 60°C for 14 h. After the reaction mixture was cooled to room temperature, THF was evaporated and the resulting aqueous solution was adjusted to pH of 4 by addition of conc. hydrochloric acid and the mixture was stirred at 120°C for 30 min. After being cooled to room temperature, the reaction mixture was neutralized with a saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated to afford an acetyl compound (2.15 g) in a yield of 49% (by a two-step process). Ethylene glycol (2.76 ml) and p-toluenesulfonic acid monohydrate (2.07 g) were successively added to a benzene solution (30 ml) of the acetyl compound (2.15 g) and the mixture was refluxed for 5 h by heating with a Dean-Stark apparatus. After the reaction mixture was cooled to room temperature, a saturated aqueous sodium carbonate solution was added and the mixture was extracted with ethyl acetate, washed with water and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated to afford a ketal benzyl compound (2.59 g) in a yield of

100%.

Palladium hydroxide on carbon (0.26 g) was added to a methanol solution (26 ml) of the ketal benzyl compound (2.59 g) and the mixture was stirred for 2 h under 3 atm hydrogen atmosphere. The palladium hydroxide on carbon was filtered off and the filtrate was concentrated under vacuum to afford a ketal compound (1.69 g) in a yield of 100%. Using this ketal compound, the procedure of Example 1 was repeated to afford the title compound.

Example 12

Preparation of (S)-N-{3-[3-fluoro-4-(3-hydroxymethyl-4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 41):

Using 600 mg of the (S)-8-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-1,4-dioxa-8-aza-spiro[4.5]decane-6-carboxylic acid methyl ester (Compound No. 36) synthesized in Example 8, reduction was performed by repeating the procedure of Example 2, thus affording an alcohol (361 mg) in a yield of 66%. Using 302 mg of the alcohol, the procedure of Example 3 was repeated to afford the title compound (155 mg) in a yield of 58%.

Example 13

Preparation of (S)-N-(3-{3-fluoro-4-[4-(2-hydroxymethyl-[1,3]dioxolan-2-yl)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide (Compound No. 48):

A ketal compound was synthesized by repeating the procedure of Example 11, except that the acetyl chloride as a feed material was replaced by benzyloxyacetyl chloride. Using this ketal, the procedure of Example 1 was repeated to synthesize a compound, from which the protective benzyl group was removed to afford the title compound.

Example 14

Preparation of (S)-N-{3-[3-fluoro-4-(2-hydroxymethyl-1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 56):

Para-toluenesulfonic acid monohydrate (299 mg) and glycerol (0.21 ml) were added successively to a benzene suspension (10 ml) of 500 mg of the (S)-N-{3-[3-fluoro-4-(4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 7) which was synthesized in Example 3, and the mixture was heated under reflux for 4 h, with water being removed continuously by means of a water separator. After the reaction mixture was cooled to room temperature, a saturated aqueous sodium hydrogencarbonate solution was added and the mixture was stirred.

Thereafter, the solution was extracted with methylene chloride and the organic layer was washed with water and brine and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum and the residue was purified by silica gel column chromatography (solvent: chloroform/methanol = 50/1 - 25/1) to afford the title compound (510 mg) in a yield of 84%.

Example 15

Preparation of (S)-N-(3-{3-fluoro-4-[4-(2-hydroxy-acetyl)-1-oxa-4,8-diaza-spiro[4.5]dec-8-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide (Compound No. 58):

Ethanolamine (0.31 ml) was added to a benzene suspension (10 ml) of 600 mg of the (S)-N-{3-[3-fluoro-4-(4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 7) which was synthesized in Example 3, and the mixture was heated under reflux for 2 h, with water being removed continuously by means of a water separator. After the reaction mixture was cooled to room temperature, the resulting crystal was collected by filtration, washed with benzene and dried under vacuum at room temperature to yield 671 mg of an oxazolidin compound. To a methylene chloride solution (5 ml) of the oxazolidin compound (671 mg), 0.17 ml of pyridine and 0.30 ml of benzyloxyacetyl chloride were added successively and the mixture was stirred at room temperature for 48 h. Following the addition of methanol, the mixture was stirred for 30 min and the solvent was evaporated. The residue was purified by silica gel column chromatography (solvent: chloroform/methanol = 50/1) to afford a benzyloxyacetyl compound (574 mg) in a yield of 62%. To a methanol-methylene chloride solution (8-4 ml) of the benzyloxyacetyl compound (574 mg), 57 mg of palladium on carbon was added and the mixture was stirred at room temperature for 14 h under 1 atm hydrogen atmosphere. After the catalyst was filtered off, the solvent was evaporated and the residue was purified by silica gel column chromatography (solvent: chloroform/methanol = 50/1 - 25/1 - 10/1) to afford the title compound (148 mg) in a yield of 31%.

Example 16

Preparation of (S)-N-{3-[3-fluoro-4-(4-methoxyamino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 63):

(S)-N-{3-[3-fluoro-4-(4-methoxyimino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 31) was synthesized using the (S)-N-{3-[3-fluoro-4-(4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 7) which was synthesized in Example 3. To a methanol solution (4

ml) of Compound No. 31 (594 mg), 0.69 ml of boran-pyridine complex (8 M) was added at 0°C and the mixture was stirred for 5 min. Thereafter, 8 ml of 10% HCl was added and the mixture was further stirred at room temperature for 15 min. After neutralization with sodium carbonate, the solution was extracted with methylene chloride and the organic layer was washed with water and brine and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum and the residue was purified by silica gel column chromatography (solvent: chloroform/methanol = 50/1) to afford the title compound (399 mg) in a yield of 67%.

Example 17

Preparation of (S)-N-(3-{4-[4-(2,3-dihydroxy-propoxyimino)-piperidin-1-yl]-3-fluoro-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide (Compound No. 66):

(S)-N-{3-[4-(4-allyloxyimino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 62) was synthesized using the (S)-N-{3-[3-fluoro-4-(4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 7) which was synthesized in Example 3. To an acetonitrile-water solution (20-2 ml) of Compound No. 62, (715 mg), 0.5 ml of osmium tetroxide (2.5 wt% tert-butanol solution) and 0.34 ml of N-methyl morpholine-N-oxide (60 wt% aq. sol.) were added successively and the mixture was stirred at room temperature for 5 h. A saturated aqueous sodium thiosulfate solution was added and the mixture was stirred for 30 min. The solution was extracted with methylene chloride-methanol and the organic layer was washed with water and brine and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum and the residue was purified by silica gel column chromatography (solvent: chloroform/methanol = 25/1 - 10/1) to afford the title compound (582 mg) in a yield of 75%.

Example 18

Preparation of (S)-N-{3-[3-fluoro-4-(4-methylamino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 70):

Methylamine hydrochloride (0.46 g) and palladium on carbon (0.20 g) were added to a methanol-methylene chloride solution (20-20 ml) of 2.00 g of the (S)-N-{3-[3-fluoro-4-(4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 7) which was synthesized in Example 3, and the mixture was stirred at room temperature for 14 h under 2 atm hydrogen atmosphere. Sodium hydrogencarbonate was added and the mixture was stirred for 10 min. Thereafter, the catalyst was filtered off and the solvent was evaporated under vacuum. The residue was purified by alumina column chromatography (solvent: chloroform/methanol = 100/1 - 30/1) to afford the title compound (900 mg) in a yield

of 43%.

Example 19

Preparation of (S)-N-{3-[4-(4-dimethylamino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 71):

Formaldehyde (37% aq. sol., 0.4 ml) and sodium cyanoboron hydride (138 mg) were successively added to an acetonitrile suspension (3 ml) of 400 mg of the (S)-N-{3-[3-fluoro-4-(4-methylamino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 70) which was synthesized in Example 18, and the mixture was stirred at room temperature for 48 h. Methanol was added and the mixture was stirred for 10 min. Thereafter, alumina (5 g) was added and the residue was evaporated under vacuum. The residue was purified by alumina column chromatography (solvent: chloroform/methanol = 100/1) to afford the title compound (363 mg) in a yield of 87%.

Example 20

Preparation of (S)-N-(3-{3-fluoro-4-[4-(thiazol-2-ylamino)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide (Compound No. 67):

Potassium carbonate (296 mg) and 2-bromothiazole (258 mg) were added to a dimethylformamide solution (5 ml) of 500 mg of the (S)-N-{3-[4-(4-amino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 6) which was synthesized in Example 4, and the mixture was stirred at 100°C for 2 days. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (dichloromethane/methanol = 97/3 - 4/1) to afford the title compound (73 mg) in a yield of 12%.

Example 21

Preparation of (S)-N-{3-[4-(4-cyanoimino-piperidin-1-yl)-3-fluoro-phenyl)-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 59):

Cyanamide (601 mg) and 500 mg of the (S)-N-{3-[3-fluoro-4-(4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 7) which was synthesized in Example 3 were added to benzene (70 ml), and the mixture was heated under reflux for 2 h, with water being removed continuously by means of a water separator. The reaction mixture was cooled to room temperature and the resulting crystal was collected by filtration. After being washed with water, the crystal was dried overnight at 40°C under vacuum to afford the title compound (423 mg) in a yield of 79%.

Example 22

Preparation of (S)-N-{3-[4-(4-dimethylaminomethyleneamino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 72):

N,N-dimethylformamide dimethylacetal (0.8 ml) and 1.0 g of the (S)-N-{3-[4-(4-amino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 6) which was synthesized in Example 4 were added to toluene (10 ml) and the mixture was heated under reflux for 24 h. The reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was washed with hexane to remove excess dimethylacetal. The resulting precipitate was suspended in dichloromethane and the insolubles were separated by filtration. The filtrate was concentrated under vacuum to afford the title compound (985 mg) in a yield of 84%.

Example 23

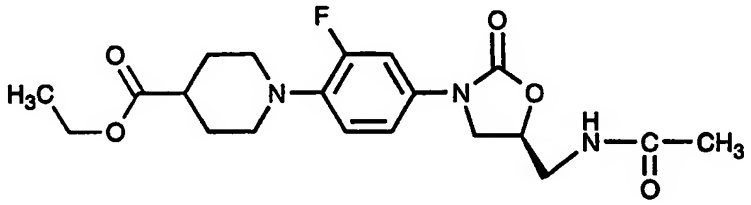
Preparation of (S)-2-fluoro-N-{3-[3-fluoro-4-(4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (Compound No. 73):

Starting with the 3-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-3-fluoro-phenyl]-5-hydroxymethyl-oxazolidin-2-one which was formed as an intermediate in Example 3, the procedure of Example 1 was repeated to produce an azide compound in a yield of 90%. The azide compound (1.5 g) was reduced with triphenylphosphine/tetrahydrofuran/water by the same method as in Example 10 to provide a primary amine compound. The amine compound and triethylamine (1.2 ml) were added to dry dichloromethane (20 ml) and benzyloxyacetyl chloride (1.20 g) was subsequently added at 0°C. The reaction mixture was stirred overnight at room temperature and the resulting precipitate was filtered off. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (methanol/dichloromethane = 5/95) to afford a benzyloxyacetamide compound (2.7 g) in a yield of 100%. The benzyloxyacetamide compound (1.9 g) was dissolved in a mixed solvent consisting of methanol (30 ml) and dichloromethane (5 ml). To the solution, 10% palladium hydroxide/carbon (340 mg) was added and the mixture was stirred for 2 days under 3 atm hydrogen atmosphere. The palladium hydroxide was filtered off and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (methanol/dichloromethane = 7/93) to afford an α-hydroxyacetamide compound (780 mg) in a yield of 49%. To a tetrahydrofuran solution (10 ml) of the α-hydroxyacetamide compound (530 mg), p-toluenesulfonyl fluoride (450 mg) and tetrabutylammonium fluoride (1.0 M tetrahydrofuran solution; 3.3 ml) were added and the mixture was heated under reflux overnight. The reaction mixture was cooled to room temperature and

concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/acetone = 2/3) to afford a monofluoroacetamide compound (562 mg) in a yield of 100%. To 10 ml of an acetone solution of the monofluoroacetamide compound, p-toluenesulfonic acid monohydrate (580 mg) and water (3 ml) were added and the mixture was heated under reflux for 2.5 h. The reaction mixture was cooled to room temperature, neutralized with solid sodium hydrogencarbonate, and concentrated under vacuum. Water was removed by azeotropy with toluene and the residue was purified by silica gel column chromatography (hexane/acetone = 1/1) to afford the title compound (408 mg) in a yield of 81%.

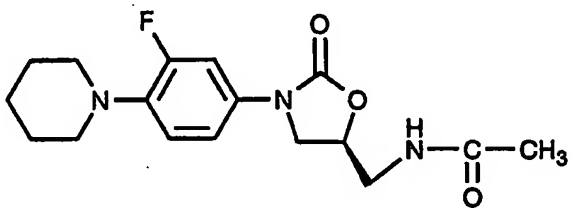
The compounds prepared in Examples 1-23, as well as several compounds that were synthesized by similar methods were found to have the following nuclear magnetic resonance spectrum (^{1}H-NMR) data.

Compound No. 1:



^{1}H NMR ($CDCl_3$) δ ppm: 1.27 (3H, t, J = 7.2 Hz), 1.86 - 2.07 (4H, m), 2.02 (3H, s), 2.37 - 2.48 (1H, m), 2.68 - 2.77 (2H, m), 3.34 - 3.41 (2H, m), 3.55 - 3.76 (3H, m), 4.01 (1H, dd, J = 8.9, 8.9 Hz), 4.16 (2H, q, J = 7.2 Hz), 4.71 - 4.81 (1H, m), 6.12 (1H, br s), 6.92 (1H, dd, J = 8.9, 8.9 Hz), 7.06 (1H, ddd, J = 2.4, 2.4, 8.9 Hz), 7.40 (1H, dd, J = 2.4, 13.8 Hz).

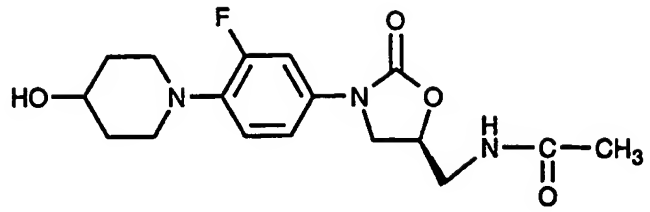
Compound No. 2



^{1}H NMR ($CDCl_3$) δ ppm: 1.52 - 1.62 (2H, m), 1.65 - 1.78 (4H, m), 2.02 (3H, s), 2.96 - 3.00 (4H, m), 3.55 - 3.77 (3H, m), 4.01 (1H, dd, J = 8.9, 8.9 Hz), 4.71 - 4.80 (1H, m), 6.28 (1H, br s), 6.93 (1H, dd, J = 8.9, 8.9 Hz), 7.05 (1H, ddd, J = 2.4, 2.4, 8.9 Hz),

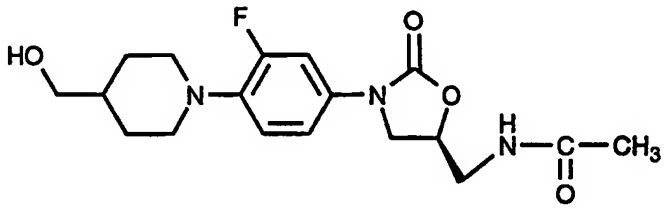
7.38 (1H, dd, J = 2.4, 14.3 Hz).

Compound No. 3



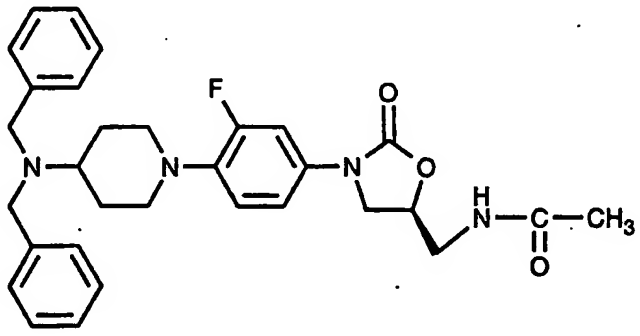
^{1}H NMR ($CDCl_3$) δ ppm: 1.69 - 1.82 (2H, m), 1.99 - 2.07 (2H, m), 2.02 (3H, s), 2.78 - 2.87 (2H, m), 3.28 - 3.35 (2H, m), 3.54 - 3.76 (3H, m), 3.81 - 3.90 (1H, m), 4.02 (1H, dd, J = 8.9, 8.9 Hz), 4.71 - 4.81 (1H, m), 6.08 (1H, t, J = 5.9 Hz), 6.94 (1H, dd, J = 8.9, 8.9 Hz), 7.06 (1H, ddd, J = 2.2, 2.2, 8.9 Hz), 7.41 (1H, dd, J = 2.2, 14.3 Hz).

Compound No. 4



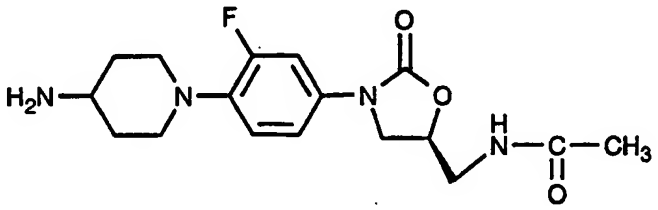
^{1}H NMR (DMSO-d_6) δ ppm: 1.22 - 1.36 (2H, m), 1.41 - 1.53 (1H, m), 1.73 - 1.77 (2H, m), 1.83 (3H, s), 2.55 - 2.63 (2H, m), 3.25 - 3.34 (4H, m), 3.39 (2H, dd, J = 5.4, 5.4 Hz), 3.69 (1H, dd, J = 6.5, 8.9 Hz), 4.07 (1H, dd, J = 8.9, 8.9 Hz), 4.48 (1H, t, J = 5.4 Hz), 4.65 - 4.74 (1H, m), 7.05 (1H, dd, J = 9.2, 9.2 Hz), 7.15 (1H, dd, J = 2.7, 9.2 Hz), 7.45 (1H, dd, J = 2.2, 14.9 Hz), 8.23 (1H, t, J = 5.9 Hz).

Compound No. 5



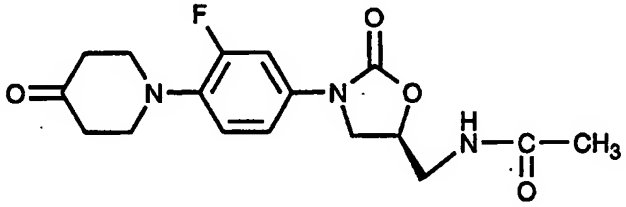
^{1}H NMR ($CDCl_3$) δ ppm: 1.84 - 1.92 (4H, m), 2.00 (3H, s), 2.49 - 2.68 (3H, m), 3.40 - 3.46 (2H, m), 3.53 - 3.74 (3H, m), 3.69 (s and s, 2H and 2H), 3.98 (1H, dd, J = 9.2, 9.2 Hz), 4.69 - 4.78 (1H, m), 6.26 (1H, t, J = 5.9 Hz), 6.87 (1H, dd, J = 9.2, 9.2 Hz), 7.01 (1H, dd, J = 2.2, 9.2 Hz), 7.16 - 7.40 (11H, m).

Compound No. 6



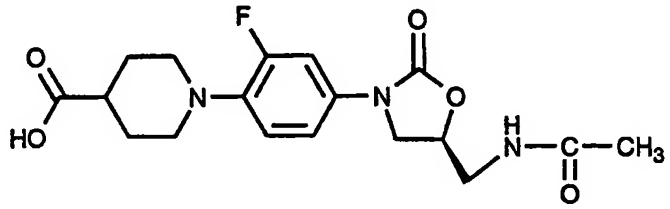
^{1}H NMR ($DMSO-d_6$) δ ppm: 1.55 - 1.69 (2H, m), 1.84 (3H, s), 1.92 - 1.99 (2H, m), 2.65 - 2.74 (2H, m), 2.98 - 3.07 (1H, m), 3.28 - 3.33 (2H, m), 3.38 - 3.74 (3H, m), 4.08 (1H, dd, J = 9.2, 9.2 Hz), 4.66 - 4.75 (1H, m), 7.07 (1H, dd, J = 9.2, 9.2 Hz), 7.17 (1H, dd, J = 2.4, 9.2 Hz), 7.47 (1H, dd, J = 2.4, 14.9 Hz), 8.28 (1H, t, J = 5.7 Hz).

Compound No. 7



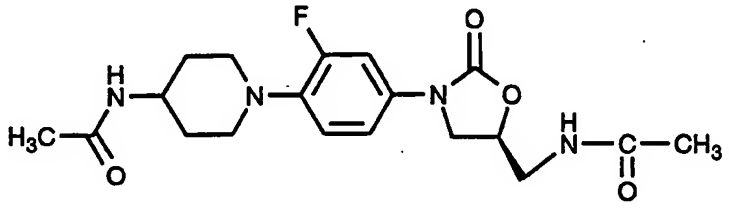
^{1}H NMR ($CDCl_3$) δ ppm: 2.03 (3H, s), 2.60 - 2.65 (4H, m), 3.35 - 3.40 (4H, m), 3.57 - 3.79 (3H, m), 4.03 (1H, dd, J = 8.9, 8.9 Hz), 4.73 - 4.82 (1H, m), 6.14 (1H, t, J = 5.9 Hz), 6.97 (1H, dd, J = 9.2, 9.2 Hz), 7.09 (1H, ddd, J = 2.2, 2.2, 9.2 Hz), 7.41 (1H, dd, J = 2.2, 14.0 Hz).

Compound No. 8



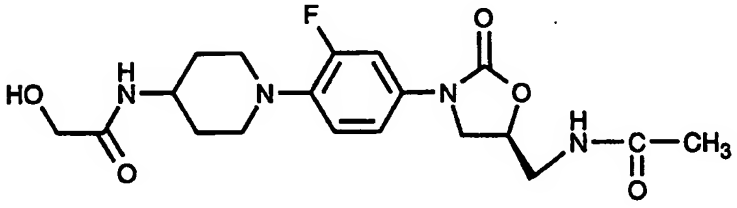
^{1}H NMR (DMSO-d_6) δ ppm: 1.60 - 1.74 (2H, m), 1.83 - 1.97 (3H, m), 1.84 (3H, s), 2.57 - 2.65 (2H, m), 3.19 - 3.25 (2H, m) 3.36 - 3.41 (2H, m), 3.73 (1H, dd, J = 6.5, 8.9 Hz), 4.07 (1H, dd, J = 8.9, 8.9 Hz), 4.65 - 4.74 (1H, m), 7.03 (1H, dd, J = 9.2, 9.2 Hz), 7.14 (1H, dd, J = 2.4, 9.2 Hz), 7.44 (1H, dd, J = 2.4, 14.9 Hz), 8.39 (1H, t, J = 5.7 Hz).

Compound No. 9



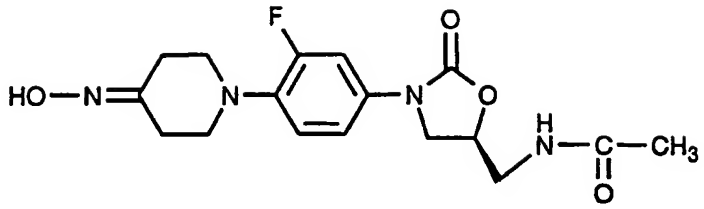
^{1}H NMR (DMSO-d_6) δ ppm: 1.45 - 1.60 (2H, m), 1.76 - 1.90 (2H, m), 1.81 (3H, s), 1.83 (3H, s), 2.67 - 2.75 (2H, m), 3.22 - 3.29 (2H, m), 3.38 - 3.42 (2H, m), 3.61 - 3.73 (2H, m), 4.08 (1H, dd, J = 9.2, 9.2 Hz), 4.66 - 4.75 (1H, m), 7.07 (1H, dd, J = 9.2, 9.2 Hz), 7.16 (1H, dd, J = 2.4, 9.2 Hz), 7.47 (1H, dd, J = 2.4, 14.9 Hz), 7.85 (1H, d, J = 8.1 Hz), 8.24 (1H, t, J = 5.7 Hz).

Compound No. 10



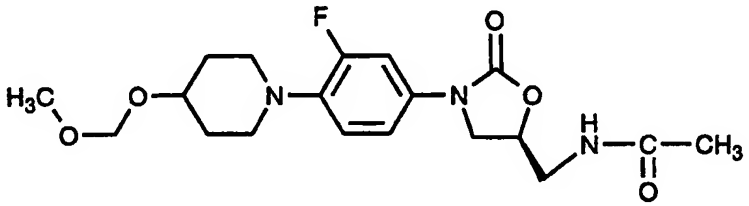
^{1}H NMR (DMSO-d_6) δ ppm: 1.71 - 1.87 (4H, m), 1.92 (3H, s), 2.76 -2.84 (2H, m), 3.32 - 3.39 (2H, m), 3.47 - 3.51 (2H, m), 3.76 - 3.86 (2H, m), 3.90 (2H, d, J = 5.9 Hz), 4.16 (1H, dd, J = 8.9, 8.9 Hz), 4.74 - 4.83 (1H, m), 5.52 (1H, t, J = 5.9 Hz), 7.15 (1H, dd, J = 9.2, 9.2 Hz), 7.24 (1H, dd, J = 1.8, 9.2 Hz), 7.55 (1H, dd, J = 1.8, 14.9 Hz), 7.74 (1H, d, J = 7.8 Hz), 8.32 (1H, t, J = 5.7 Hz).

Compound No. 11



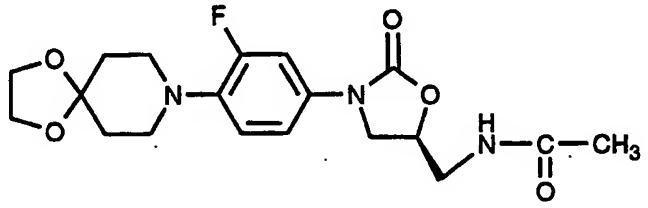
^{1}H NMR (DMSO-d_6) δ ppm: 1.83 (3H, s), 2.25 - 2.38 (2H, m), 2.61 - 2.65 (2H, m), 3.00 - 3.11 (4H, m), 3.38 - 3.42 (2H, m), 3.70 (1H, dd, J = 6.5, 9.2 Hz), 4.08 (1H, dd, J = 9.2, 9.2 Hz), 4.64 - 4.75 (1H, m), 7.09 (1H, dd, J = 8.9, 8.9 Hz), 7.17 (1H, dd, J = 2.2, 8.9 Hz), 7.49 (1H, dd, J = 2.2, 14.9 Hz) 8.24 (1H, t, J = 4.9 Hz), 10.42 (1H, s).

Compound No. 29



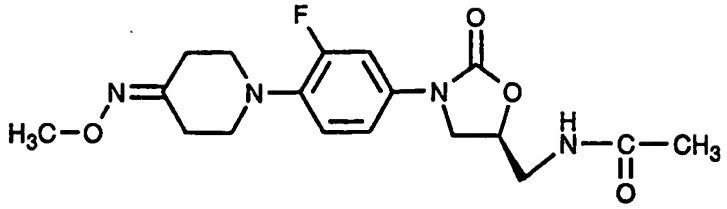
^{1}H NMR ($CDCl_3$) δ ppm: 1.71 - 1.88 (2H, m), 2.00 - 2.10 (2H, m), 2.02 (3H, s), 2.79 - 2.88 (2H, m), 3.26 - 3.37 (2H, m), 3.40 (3H, s), 3.55 - 3.77 (4H, m), 4.01 (1H, dd, J = 8.9, 8.9 Hz), 4.70 - 4.81 (1H, m), 4.73 (2H, s), 6.22 (1H, br s), 6.94 (1H, dd, J = 9.2, 9.2 Hz), 7.05 (1H, ddd, J = 1.5, 1.5, 8.9 Hz), 7.40 (1H, dd, J = 2.4, 14.3 Hz).

Compound No. 30



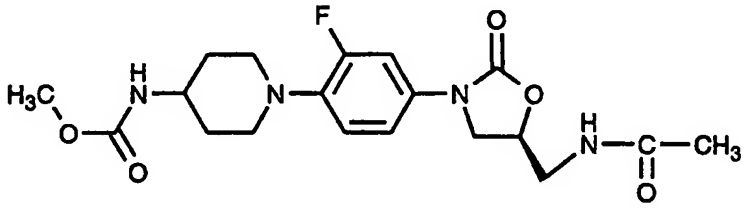
^{1}H NMR ($CDCl_3$) δ ppm: 1.87 - 1.91 (4H, m), 2.02 (3H, s), 3.11 - 3.15 (2H, m), 3.56 - 3.78 (3H, m), 4.00 (4H, s), 4.01 (1H, t, J = 8.9 Hz), 4.72 - 4.81 (1H, m), 6.49 (1H, t, J = 6.2 Hz), 6.94 (1H, dd, J = 8.9, 8.9 Hz), 7.04 (1H, dd, J = 3.0, 8.9 Hz), 7.39 (1H, dd, J = 2.6, 14.2 Hz).

Compound No. 31



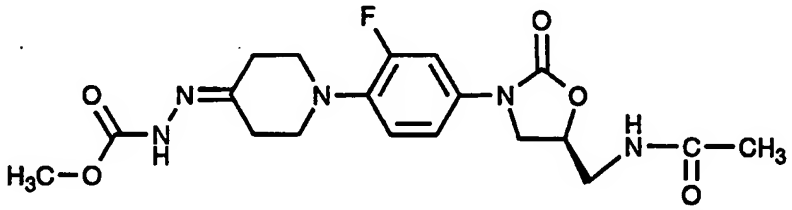
^{1}H NMR ($CDCl_3$) δ ppm: 2.02 (3H, s), 2.48 - 2.52 (2H, m), 2.72 - 2.77 (2H, m), 3.09 - 3.13 (2H, m), 3.16 - 3.20 (2H, m), 3.56 - 3.69 (2H, m), 3.75 (1H, dd, J = 6.8, 9.2 Hz), 3.86 (3H, s), 4.02 (1H, dd, J = 9.2, 9.2 Hz), 4.72 - 4.82 (1H, m), 6.25 (1H, br s), 6.92 (1H, dd, J = 8.9, 8.9 Hz), 7.06 (1H, dd, J = 2.6, 8.8 Hz), 7.43 (1H, dd, J = 2.4, 14.3 Hz).

Compound No. 32



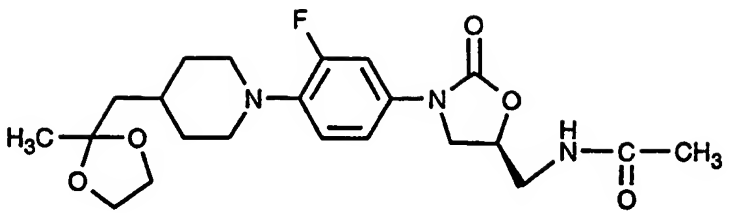
^{1}H NMR (DMSO-d_6) δ ppm: 1.49 - 1.61 (2H, m), 1.80 - 1.90 (2H, m), 1.83 (3H, s), 2.66 - 2.73 (2H, m), 3.23 - 3.31 (2H, m), 3.38 - 3.42 (2H, m), 3.53 (3H, s), 3.69 (1H, dd, J = 6.5, 8.9 Hz), 4.07 (1H, dd, J = 9.0, 9.0 Hz), 4.65 - 4.73 (1H, m), 7.07 (1H, dd, J = 9.5, 9.5 Hz), 7.15 (1H, dd, J = 2.2, 9.2 Hz), 7.46 (1H, dd, J = 2.4, 14.9 Hz), 8.23 (1H, t, J = 5.7 Hz).

Compound No. 33



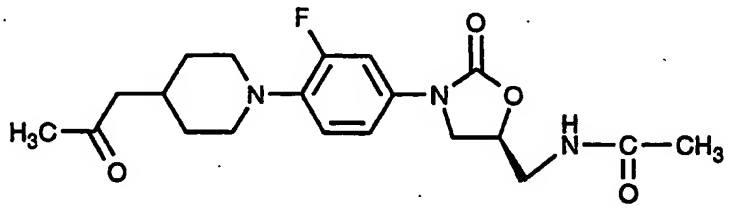
^{1}H NMR (DMSO-d_6) δ ppm: 1.83 (3H, s), 2.42 - 2.46 (2H, m), 2.56 - 2.60 (2H, m), 3.03 - 3.07 (2H, m), 3.10 - 3.15 (2H, m), 3.38 - 3.42 (2H, m), 3.70 (1H, dd, J = 6.3, 8.8 Hz), 4.08 (1H, dd, J = 8.9, 8.9 Hz), 4.66 - 4.75 (1H, m), 7.09 (1H, dd, J = 9.0, 9.0 Hz), 7.17 (1H, dd, J = 2.4, 8.9 Hz), 7.49 (1H, dd, J = 2.4, 14.6 Hz) 8.23 (1H, t, J = 5.8 Hz).

Compound No. 34



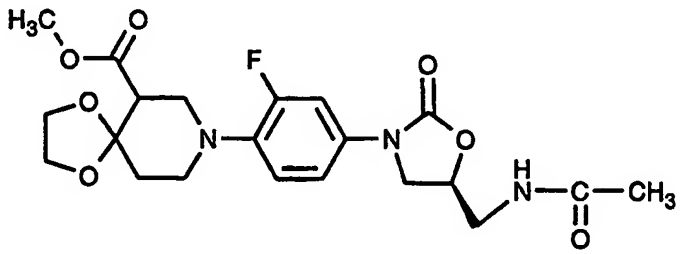
^{1}H NMR ($CDCl_3$) δ ppm: 1.35 (3H, s), 1.40 - 1.75 (5H, m), 1.90 (2H, d, J = 12.2 Hz), 2.02 (3H, s), 2.60 - 2.68 (2H, m), 3.33 - 3.38 (2H, m), 3.55 - 3.77 (3H, m), 3.90 - 3.96 (4H, m), 4.01 (1H, dd, J = 8.8, 8.8 Hz), 4.71 - 4.80 (1H, m), 6.34 (1H, br s), 6.92 (1H, dd, J = 8.9, 8.9 Hz), 7.05 (1H, br d, J = 8.9 Hz), 7.38 (1H, dd, J = 2.4, 14.6 Hz).

Compound No. 35



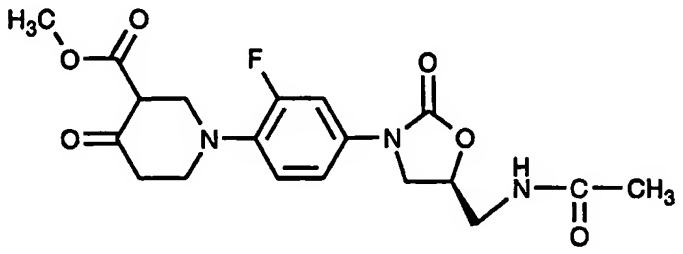
^{1}H NMR ($CDCl_3$) δ ppm: 1.36 - 1.51 (2H, m), 1.77 - 1.82 (2H, m), 1.91 - 2.05 (1H, m), 2.02 (3H, s), 2.16 (3H, s), 2.43 (2H, d, J = 6.8 Hz), 2.63 - 2.72 (2H, m), 3.34 - 3.38 (2H, m), 3.55 - 3.77 (3H, m), 4.01 (1H, dd, J = 9.0, 9.0 Hz), 4.72 -4.81 (1H, m), 6.28 (1H, br s), 6.92 (1H, dd, J = 9.0, 9.0 Hz), 7.05 (1H, ddd, J = 1.5, 1.5, 8.9 Hz), 7.39 (1H, dd, J = 2.3, 14.2 Hz).

Compound No. 36



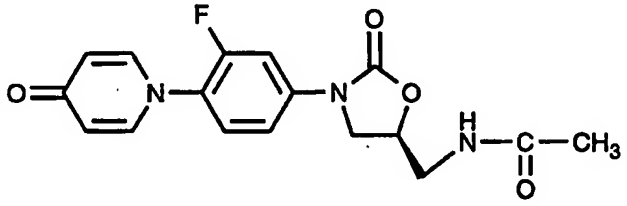
^{1}H NMR ($CDCl_3$) δ ppm: 1.66 - 1.92 (1H, m), 1.93 (3H, s), 2.02 - 2.09 (1H, m), 2.97 - 3.12 (2H, m), 3.23 (1H, m), 3.39 (2H, d, J = 6.8 Hz), 3.57 - 3.77 (3H, m), 3.74 (3H, s), 4.02 (5H, m), 4.77 (1H, m), 6.20 (1H, t, J = 5.9 Hz), 6.95 (1H, t, J = 8.6 Hz), 7.05 (1H, dd, J = 2.4, 8.6 Hz), 7.41 (1H, dd, J = 2.4, 13.8 Hz).

Compound No. 37



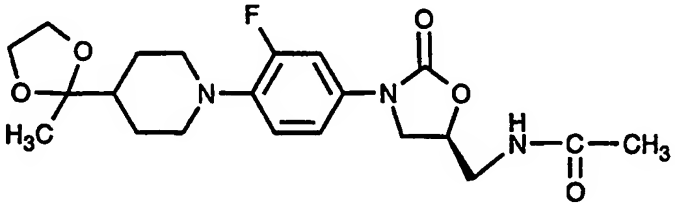
^{1}H NMR ($CDCl_3$) δ ppm: 2.02 (3H, s), 2.49 - 2.74 (2H, m), 3.27 - 3.39 (2H, m), 3.57 - 3.71 (4H, m), 3.73 (2H, d, J = 6.8 Hz), 3.78 (3H, s), 4.02 (1H, t, J = 8.9 Hz), 4.78 (1H, m), 6.45 (1H, broad), 6.97 (1H, t, J = 8.6 Hz), 7.06 (1H, dd, J = 2.4, 8.6 Hz), 7.43 (1H, dd, J = 2.4, 13.8 Hz).

Compound No. 38



^{1}H NMR ($CDCl_3$) δ ppm: 2.04 (3H, s), 3.68 (2H, t, J = 5.7 Hz), 3.89 (1H, dd, J = 6.8, 9.5 Hz), 4.11 (1H, t, J = 9.5 Hz), 4.85 (1H, m), 6.50 (2H, d, J = 7.8 Hz), 7.15 (1H, t, J = 5.9 Hz), 7.34 (1H, dd, J = 2.4, 8.6 Hz), 7.38 (1H, t, J = 8.6 Hz), 7.47 (2H, d, J = 7.8 Hz), 7.74 (1H, dd, J = 2.4, 13.8 Hz).

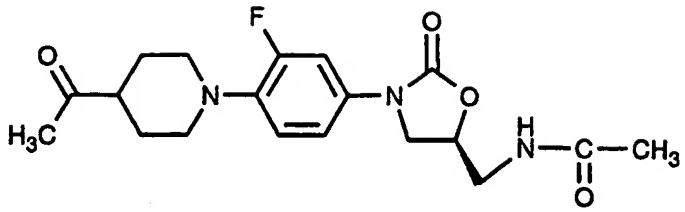
Compound No. 39



^{1}H NMR ($CDCl_3$) δ ppm: 1.30 (3H, s), 1.60 - 1.88 (5H, m), 2.02 (3H, s), 2.55 - 2.64 (2H, m), 3.44 - 3.48 (2H, m), 3.55 - 3.77 (3H, m), 3.89 - 4.04 (5H, m), 4.72 - 4.81 (1H, m), 6.39 (1H, br s), 6.92 (1H, dd, J = 9.0, 9.0 Hz), 7.05 (1H, dd, J = 2.2, 9.2 Hz), 7.38

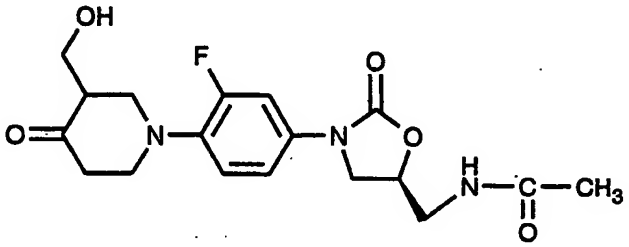
(1H, dd, J = 2.8, 14.2 Hz).

Compound No. 40



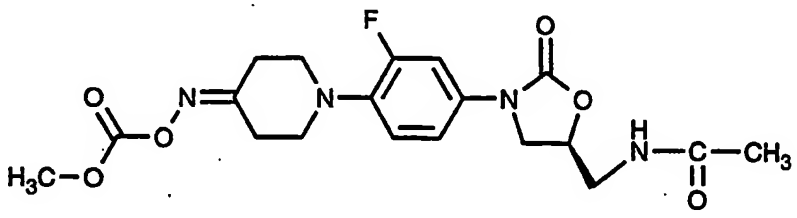
^{1}H NMR ($CDCl_3$) δ ppm: 1.76 - 2.00 (4H, m), 2.02 (3H, s), 2.19 (3H, s), 2.38 - 2.49 (1H, m), 2.66 - 2.76 (2H, m), 3.40 - 3.44 (2H, m), 3.56 - 3.77 (3H, m), 4.01 (1H, dd, J = 8.8, 8.8 Hz), 4.72 - 4.81 (1H, m), 6.35 (1H, br s), 6.92 (1H, dd, J = 8.9, 8.9 Hz), 7.05 (1H, brd, J = 8.9 Hz), 7.39 (1H, dd, J = 2.2, 14.6 Hz).

Compound No. 41



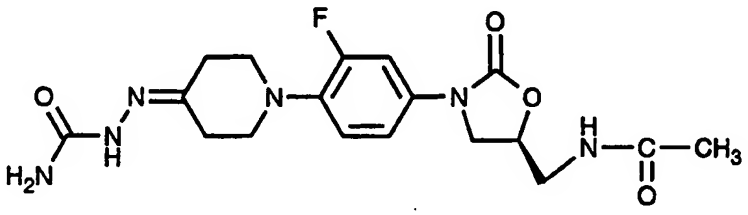
^{1}H NMR ($CDCl_3$) δ ppm: 2.02 (3H, s), 2.54 (1H, m), 2.64 - 2.92 (2H, m), 3.05 - 3.20 (2H, m), 3.57 - 4.06 (7H, m), 4.03 (1H, t, J = 9.2 Hz), 4.78 (1H, m), 6.27 (1H, br s), 6.98 (1H, t, J = 8.6 Hz), 7.08 (1H, dd, J = 2.4, 8.6 Hz), 7.47 (1H, dd, J = 2.4, 13.8 Hz).

Compound No. 42



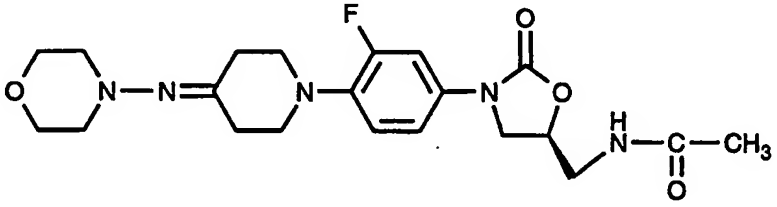
^{1}H NMR ($CDCl_3$) δ ppm: 2.02 (3H, s), 2.66 - 2.70 (2H, m), 2.84 - 2.88 (2H, m), 3.15 - 3.19 (2H, m), 3.23 - 3.27 (2H, m), 3.56 - 3.78 (3H, m), 3.90 (3H, s), 4.02 (1H, dd, J = 9.0, 9.0 Hz), 4.73 - 4.82 (1H, m), 6.15 (1H, br s), 6.93 (1H, dd, J = 9.0, 9.0 Hz), 7.07 (1H, ddd, J = 1.1, 1.1, 8.9 Hz), 7.46 (1H, dd, J = 2.6, 14.2 Hz).

Compound No. 43



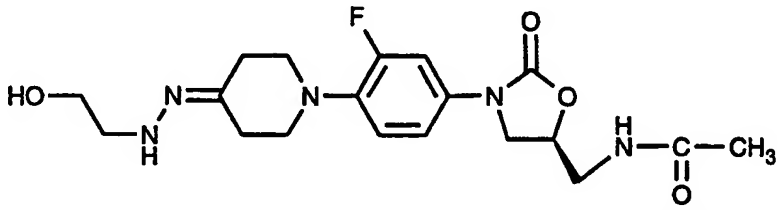
^{1}H NMR (DMSO-d_6) δ ppm: 1.83 (3H, s), 2.42 - 2.46 (2H, m), 2.55 - 2.60 (2H, m), 3.03 - 3.07 (2H, m), 3.10 - 3.14 (2H, m), 3.38 - 3.42 (2H, m), 3.70 (1H, dd, J = 6.2, 9.2 Hz), 3.90 (3H, s), 4.08 (1H, dd, J = 9.0, 9.0 Hz), 4.66 - 4.73 (1H, m), 6.23 (2H, s), 7.09 (1H, dd, J = 8.9, 8.9 Hz), 7.17 (1H, dd, J = 2.4, 8.9 Hz), 7.49 (1H, dd, J = 2.4, 14.6 Hz) 8.23 (1H, t, J = 5.7 Hz), 9.25 (1H, s).

Compound No. 44



^{1}H NMR (DMSO-d_6) δ ppm: 1.83 (3H, s), 2.41 (2H, t, J = 5.9 Hz), 2.62 (4H, m), 2.73 (2H, t, J = 5.9 Hz), 3.06 (2H, t, J = 5.9 Hz), 3.12 (2H, t, J = 5.9 Hz), 3.40 (2H, t, J = 5.4 Hz), 3.66 (5H, m), 4.08 (1H, t, J = 8.9 Hz), 4.70 (1H, m), 7.09 (1H, t, J = 9.2 Hz), 7.17 (1H, dd, J = 2.4, 9.2 Hz), 7.49 (1H, dd, J = 2.2, 14.9 Hz), 8.23 (1H, t, J = 5.7 Hz).

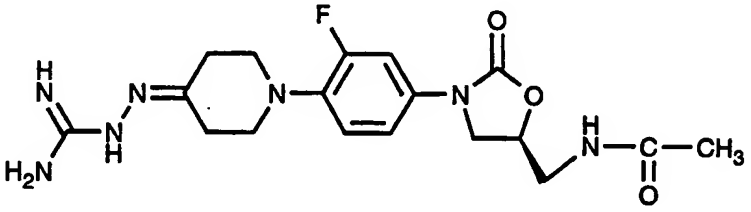
Compound No. 45



^{1}H NMR (DMSO-d_6) δ ppm: 1.83 (3H, s), 2.35 (2H, t, J = 5.7 Hz), 2.43 (2H, t, J = 5.7 Hz), 3.06 (6H, m), 3.40 (2H, t, J = 5.9 Hz), 3.50 (2H, dd, J = 5.9, 11.9 Hz), 3.70

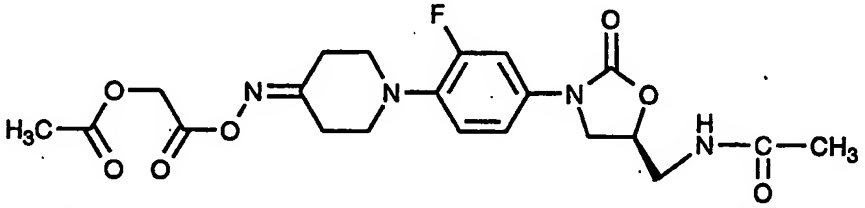
(1H, dd, J = 6.5, 8.9 Hz), 4.08 (1H, t, J = 8.9 Hz), 4.67 (1H, t, J = 5.4 Hz), 4.71 (1H, m), 5.77 (1H, t, J = 4.9 Hz), 7.07 (1H, t, J = 9.2 Hz), 7.16 (1H, dd, J = 2.4, 9.2 Hz), 7.48 (1H, dd, J = 2.2, 14.9 Hz), 8.23 (1H, t, J = 5.7 Hz).

Compound No. 46



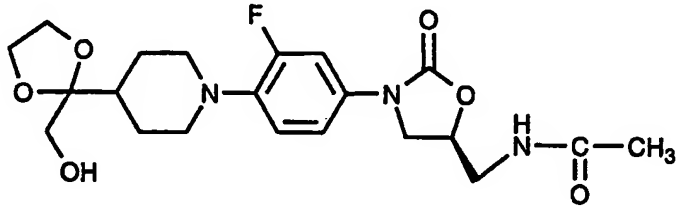
^{1}H NMR (DMSO-d_6) δ ppm: 1.83 (3H, s), 2.42 - 2.47 (2H, m), 2.73 - 2.77 (2H, m), 3.01 - 3.05 (2H, m), 3.09 - 3.12 (2H, m), 3.38 -3.42 (2H, m), 3.71 (1H, dd, J = 6.2, 9.5 Hz), 4.08 (1H, dd, J = 9.0, 9.0 Hz), 4.66 - 4.75 (1H, m), 5.88 (3H, br s), 7.09 (1H, dd, J = 9.3, 9.3 Hz), 7.16 (1H, dd, J = 2.4, 8.6 Hz), 7.49 (1H, dd, J = 2.3, 14.7 Hz) 8.25 (1H, t, J = 5.7 Hz).

Compound No. 47



^{1}H NMR ($CDCl_3$) δ ppm: 2.02 (3H, s), 2.19 (3H, s), 2.65 - 2.69 (2H, m), 2.81 - 2.86 (2H, m), 3.16 - 3.20 (2H, m), 3.23 - 3.27 (2H, m), 3.57 - 3.79 (3H, m), 4.02 (1H, dd, J = 9.0, 9.0 Hz), 4.73 - 4.82 (1H, m), 4.79 (2H, s), 6.25 (1H, t, J = 6.3 Hz), 6.93 (1H, dd, J = 8.9, 8.9 Hz), 7.08 (1H, ddd, J = 1.2, 1.2, 8.8 Hz), 7.46 (1H, dd, J = 2.4, 14.0 Hz).

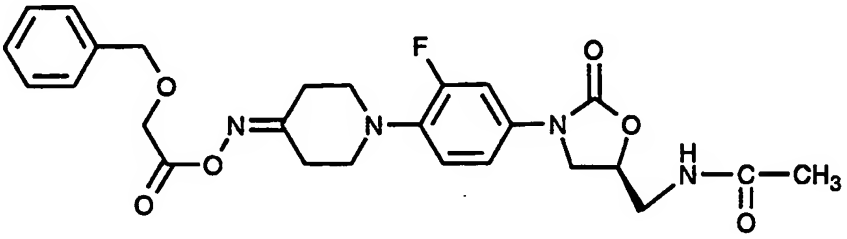
Compound No. 48



^{1}H NMR (DMSO-d_6) δ ppm: 1.42 - 1.54 (2H, m), 1.72 - 1.89 (3H, m), 1.83 (3H, s),

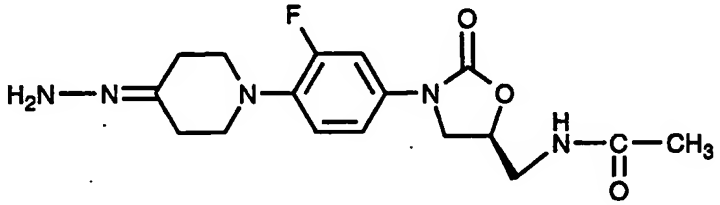
2.51 - 2.59 (2H, m), 3.32 - 3.42 (4H, m), 3.69 (1H, dd, J = 6.6, 9.0 Hz), 3.82 - 3.96 (4H, m), 4.07 (1H, dd, J = 9.0, 9.0 Hz), 4.65 - 4.75 (1H, m), 4.75 (1H, t, J = 6.1 Hz), 7.04 (1H, dd, J = 9.3, 9.3 Hz), 7.14 (1H, dd, J = 2.4, 8.6 Hz), 7.45 (1H, dd, J = 2.4, 15.1 Hz), 8.23 (1H, t, J = 5.8 Hz).

Compound No. 49



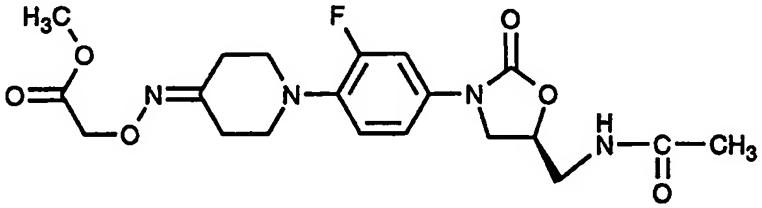
^{1}H NMR ($CDCl_3$) δ ppm: 2.02 (3H, s), 2.65 - 2.70 (2H, m), 2.80 - 2.84 (2H, m), 3.13 - 3.18 (2H, m), 3.22 - 3.26 (2H, m), 3.56 - 3.79 (3H, m), 4.01 (1H, dd, J = 9.0, 9.0 Hz), 4.27 (2H, s), 4.69 (2H, s), 4.72 - 4.82 (1H, m), 6.33 (1H, t, J = 6.3 Hz), 6.92 (1H, dd, J = 9.0, 9.0 Hz), 7.07 (1H, dd, J = 2.0, 8.8 Hz), 7.29 - 7.48 (6H, m).

Compound No. 50



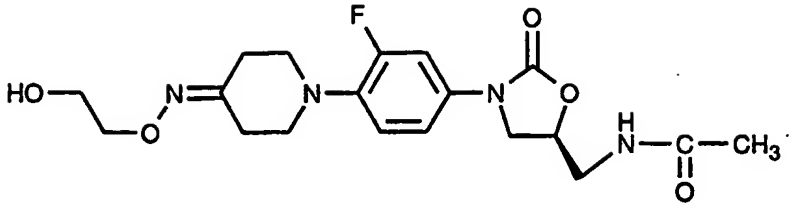
^{1}H NMR (DMSO-d_6) δ ppm: 1.83 (3H, s), 2.54 (2H, t, J = 5.4 Hz), 2.69 (2H, t, J = 5.4 Hz), 3.06 (2H, t, J = 5.4 Hz), 3.18 (2H, t, J = 5.4 Hz), 3.40 (2H, t, J = 5.4 Hz), 3.71 (1H, dd, J = 6.2, 8.6 Hz), 4.08 (1H, t, J = 8.6 Hz), 4.70 (1H, m), 7.11 (1H, t, J = 9.2 Hz), 7.17 (1H, dd, J = 2.4, 9.2 Hz), 7.49 (1H, dd, J = 2.2, 14.9 Hz), 8.23 (1H, t, J = 5.9 Hz).

Compound No. 51



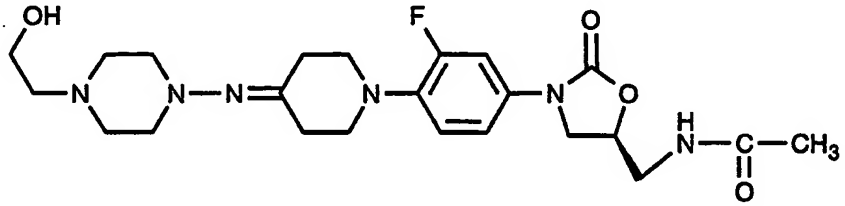
^{1}H NMR ($CDCl_3$) δ ppm: 2.02 (3H, s), 2.48 - 2.52 (2H, m), 2.81 - 2.86 (2H, m), 3.13 - 3.23 (4H, m), 3.56 - 3.78 (3H, m), 3.77 (3H, s), 4.05 (1H, dd, J = 8.4, 8.4 Hz), 4.61 (2H, s), 4.73 - 4.82 (1H, m), 6.32 (1H, t, J = 5.8 Hz), 6.93 (1H, dd, J = 9.0, 9.0 Hz), 7.06 (1H, dd, J = 1.5, 8.8 Hz), 7.43 (dd, 1H, J = 2.6, 14.2 Hz).

Compound No. 52



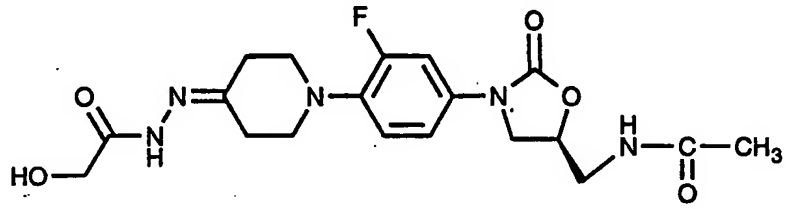
^{1}H NMR ($CDCl_3$) δ ppm: 2.02 (3H, s), 2.48 - 2.53 (2H, m), 2.76 - 2.80 (2H, m), 3.11 - 3.21 (4H, m), 3.56 - 3.78 (3H, m), 3.87 - 3.92 (2H, m), 4.02 (1H, dd, J = 9.0, 9.0 Hz), 4.16 -4.19 (2H, m), 4.72 - 4.82 (1H, m), 6.12 (1H, t, J = 6.1 Hz), 6.93 (1H, dd, J = 9.0, 9.0 Hz), 7.09 (1H, dd, J = 1.4, 8.6 Hz), 7.44 (dd, 1H, J = 2.6, 13.9 Hz).

Compound No. 53



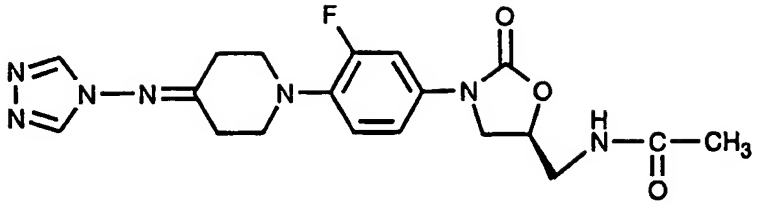
^{1}H NMR ($CDCl_3$) δ ppm: 2.02 (3H, s), 2.54 - 2.84 (14H, m), 3.14 (2H, t, J = 5.7 Hz), 3.22 (2H, t, J = 5.7 Hz), 3.61 (4H, m), 3.75 (1H, dd, J = 6.2, 8.6 Hz), 4.02 (1H, t, J = 8.6 Hz), 4.78 (1H, m), 6.13 (1H, br s), 6.93 (1H, t, J = 8.6 Hz), 7.07 (1H, dd, J = 2.4, 8.6 Hz), 7.44 (1H, dd, J = 2.4, 13.8 Hz).

Compound No. 54



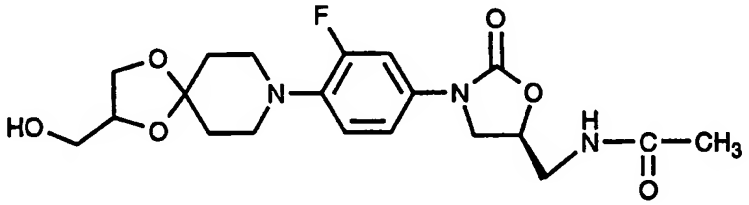
^{1}H NMR (DMSO-d_6) δ ppm: 1.83 (3H, s), 2.55 (4H, m), 3.03 (2H, m), 3.19 (2H, m), 3.40 (2H, m), 3.70 (1H, m), 4.08 (1H, t, J = 9.2 Hz), 4.12 (2H, s), 4.71 (1H, m), 7.13 (2H, m), 7.48 (1H, dd, J = 2.2, 14. 9 Hz), 8.23 (1H, t, J = 5.7 Hz).

Compound No. 55



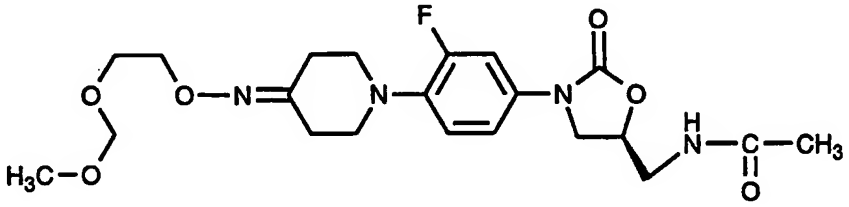
^{1}H NMR ($CDCl_3$ + CD_3OD) δ ppm: 2.02 (3H, s), 2.63 - 2.68 (2H, m), 2.85 - 2.89 (2H, m), 3.18 - 3.22 (2H, m), 3.35 - 3.40 (2H, m), 3.54 - 3.80 (3H, m), 4.04 (1H, dd, J = 9.0, 9.0 Hz), 4.73 - 4.82 (1H, m), 6.96 (1H, dd, J = 9.0, 9.0 Hz), 7.10 (1H, ddd, J = 1.2, 1.2, 8.6 Hz), 7.30 (1H, br s), 7.47 (1H, dd, J = 2.4, 14.0 Hz), 8.22 (2H, s).

Compound No. 56



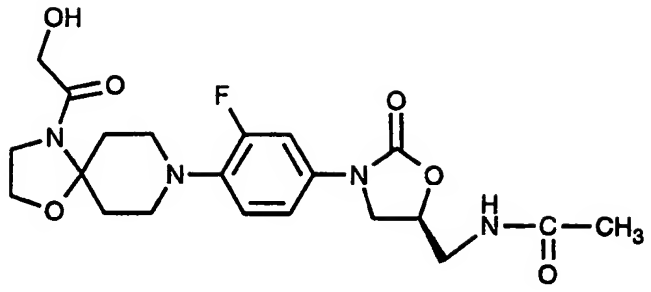
^{1}H NMR (DMSO-d_6) δ ppm: 1.64 - 1.70 (4H, m), 1.83 (3H, s), 2.98 - 3.07 (4H, m), 3.38 - 3.51 (4H, m), 3.67 - 3.74 (2H, m), 3.99 - 4.14 (3H, m), 4.67 - 4.72 (1H, m), 4.84 (1H, t, J = 5.5 Hz), 7.05 - 7.18 (2H, m), 7.46 (1H, dd, J = 2.4, 14.6 Hz), 8.23 (1H, t, J = 5.8 Hz).

Compound No. 57



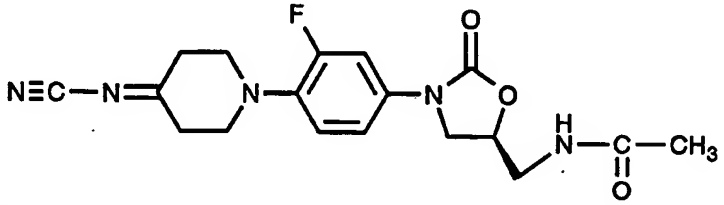
^{1}H NMR ($CDCl_3$) δ ppm: 2.02 (3H, s), 2.48 - 2.53 (2H, m), 2.77 - 2.81 (2H, m), 3.09 - 3.20 (4H, m), 3.38 (3H, s), 3.56 - 3.81 (5H, m), 4.02 (1H, dd, J = 9.0, 9.0 Hz), 4.21 - 4.25 (1H, m), 4.68 (2H, s), 4.72 - 4.82 (1H, m), 6.22 (1H, t, J = 6.2 Hz), 6.92 (1H, dd, J = 9.0, 9.0 Hz), 7.07 (1H, dd, J = 2.2, 9.5 Hz), 7.43 (1H, dd, J = 2.4, 14.0 Hz).

Compound No. 58



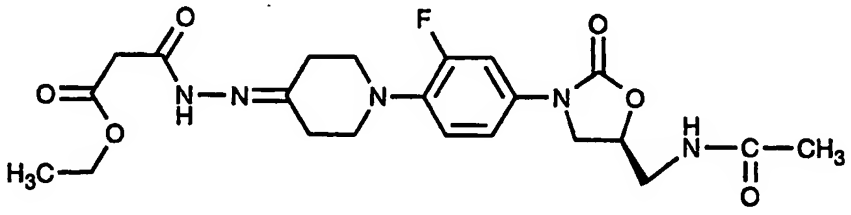
^{1}H NMR (DMSO-d_6) δ ppm: 1.52 - 1.57 (2H, m), 1.83 (3H, s), 2.73 - 2.92 (4H, m), 3.22 - 3.26 (2H, m), 3.38 - 3.42 (2H, m), 3.51 - 3.58 (2H, m), 3.67 - 3.73 (1H, m), 3.97 - 4.12 (5H, m), 4.62 - 4.75 (2H, m), 7.05 - 7.18 (2H, m), 7.47 (1H, dd, J = 2.4, 15.1 Hz), 8.23 (1H, t, J = 5.8Hz).

Compound No. 59



^{1}H NMR (DMSO-d_6) δ ppm: 1.83 (3H, s), 1.78 - 2.18 (4H, m), 3.10 - 3.21 (4H, m), 3.38 (2H, m), 3.70 (1H, dd, J = 6.2, 9.2 Hz), 4.08 (1H, t, J = 9.2 Hz), 4.71 (1H, m), 7.00 - 7.20 (2H, m), 7.48 (1H, dd, J = 2.4, 14.0 Hz), 8.23 (1H, t, J = 5.9 Hz).

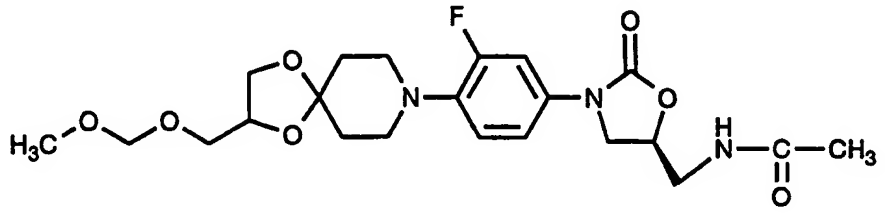
Compound No. 60



^{1}H NMR ($CDCl_3$) δ ppm: 1.27 and 1.32 (each, t, J = 7.0 H, total 3H), 2.02 (3H, s), 2.54 - 2.75 (4H, m), 3.15 - 3.26 (4H, m), 3.63 - 3.71 (2H, m), 3.76 (1H, dd, J = 6.8, 9.3

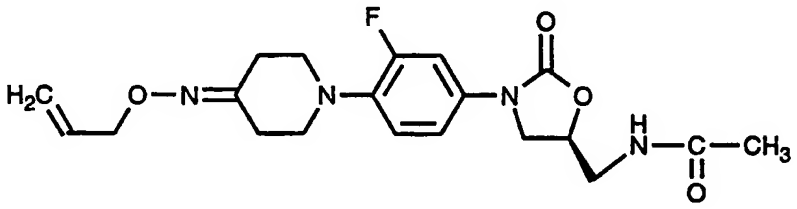
Hz), 4.02 (1H, t, J = 9.3 Hz), 4.21 and 4.25 (each q, J = 7.0 Hz, total 2H), 4.77 (1H, m), 6.23 (1H, br s), 6.93 (1H, t, J = 8.9 Hz), 7.07 (1H, dd, J = 2.4, 8.9 Hz), 7.45 (1H, dd, J = 2.4, 14.0 Hz).

Compound No. 61



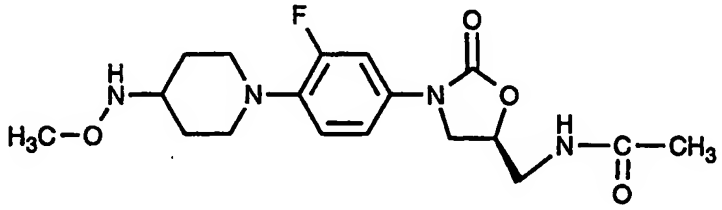
^{1}H NMR ($CDCl_3$) δ ppm: 1.85 - 1.97 (4H, m), 2.02 (3H, s), 3.09 - 3.18 (4H, m), 3.38 (3H, s), 3.54 - 3.84 (6H, m), 4.01 (1H, dd, J = 9.0, 9.0 Hz), 4.12 (1H, dd, J = 6.5, 8.4 Hz), 4.31 - 4.40 (1H, m), 4.67 (2H, s), 4.72 - 4.82 (1H, m), 6.15 (1H, br s), 6.94 (1H, dd, J = 9.0, 9.0 Hz), 7.05 (1H, dd, J = 1.9, 8.9 Hz), 7.40 (1H, dd, J = 2.6, 14.2 Hz).

Compound No. 62



^{1}H NMR ($CDCl_3$) δ ppm: 2.02 (3H, s), 2.49 - 2.53 (2H, m), 2.77 - 2.81 (2H, m), 3.10 - 3.23 (4H, m), 3.56 - 3.78 (3H, m), 4.02 (1H, dd, J = 8.6, 8.6 Hz), 4.56 (2H, dd, J = 1.6, 5.9 Hz), 4.72 - 4.82 (1H, m), 5.22 (1H, dd, J = 1.4, 10.8 Hz), 5.30 (1H, dd, J = 1.4, 18.9 Hz), 5.94 - 6.08 (1H, m), 6.30 (1H, t, J = 6.3 Hz), 6.92 (1H, dd, J = 9.0, 9.0 Hz), 7.06 (1H, dd, J = 2.4, 8.6 Hz), 7.43 (1H, dd, J = 2.4, 14.0 Hz).

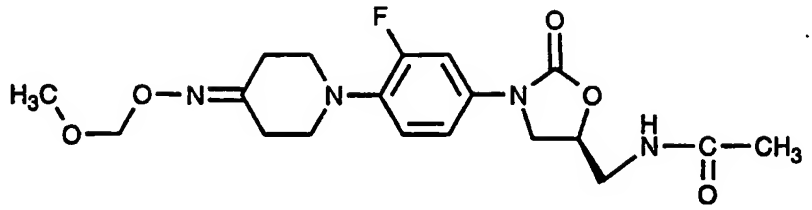
Compound No. 63



^{1}H NMR ($CDCl_3$) δ ppm: 1.54 - 1.68 (2H, m), 1.96 - 2.01 (2H, m), 2.02 (3H, s), 2.69 - 2.78 (2H, m), 2.96 - 3.07 (1H, m), 3.37 - 3.42 (2H, m), 3.57 (3H, s), 3.60 - 3.77 (3H, m), 4.01 (1H, dd, J = 9.0, 9.0 Hz), 4.72 - 4.81 (1H, m), 6.22 (1H, t, J = 5.8 Hz), 6.94

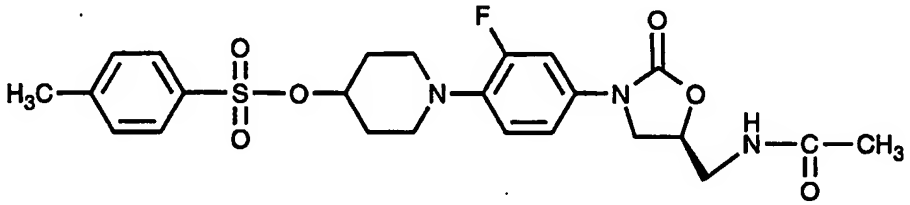
(1H, dd, J = 9.0, 9.0 Hz), 7.05 (1H, dd, J = 2.3, 9.0 Hz), 7.39 (1H, dd, J = 2.3, 14.2 Hz).

Compound No. 64



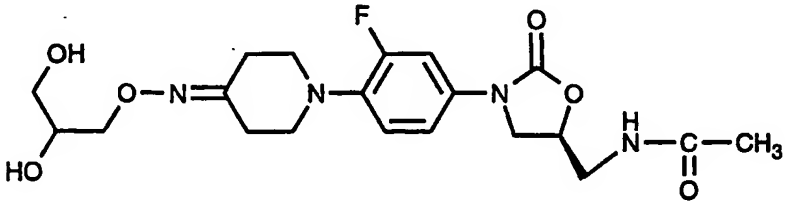
^{1}H NMR ($CDCl_3$) δ ppm: 2.02 (3H, s), 2.52 - 2.57 (2H, m), 2.79 - 2.83 (2H, m), 3.11 - 3.22 (4H, m), 3.44 (3H, s), 3.56 - 3.78 (3H, m), 4.02 (1H, dd, J = 8.9, 8.9 Hz), 4.72 - 4.82 (1H, m), 5.09 (2H, s), 6.23 (1H, t, J = 6.3 Hz), 6.93 (1H, dd, J = 9.3, 9.3 Hz), 7.07 (1H, ddd, J = 1.5, 1.5, 8.6 Hz), 7.44 (1H, dd, J = 2.4, 14.0 Hz).

Compound No. 65



^{1}H NMR ($CDCl_3$) δ ppm: 1.91 - 2.02 (4H, m), 1.99 (3H, s), 2.46 (3H, s), 2.85 - 2.94 (2H, m), 3.15 - 3.23 (2H, m), 3.56 - 3.68 (2H, m), 3.74 (1H, dd, J = 6.8, 9.3 Hz), 4.00 (1H, t, J = 9.3 Hz), 7.04 (1H, dd, J = 2.4, 9.5 Hz), 7.32 (2H, d, J = 6.5 Hz), 7.40 (1H, dd, J = 2.4, 14.0 Hz), 7.87 (2H, d, J = 6.5 Hz).

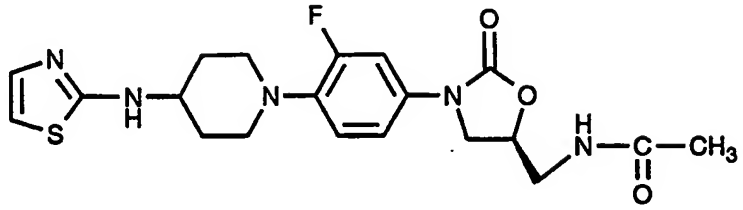
Compound No. 66



^{1}H NMR (DMSO-d_6) δ ppm: 1.83 (3H, s), 2.37 - 2.41 (2H, m), 2.64 - 2.68 (2H, m), 3.02 - 3.13 (4H, m), 3.34 - 3.42 (4H, m), 3.67 - 3.73 (2H, m), 3.86 (1H, dd, J = 6.3, 10.7 Hz), 3.98 (1H, dd, J = 5.0, 10.7 Hz), 4.08 (1H, dd, J = 9.0, 9.0 Hz), 4.53 (1H, t, J

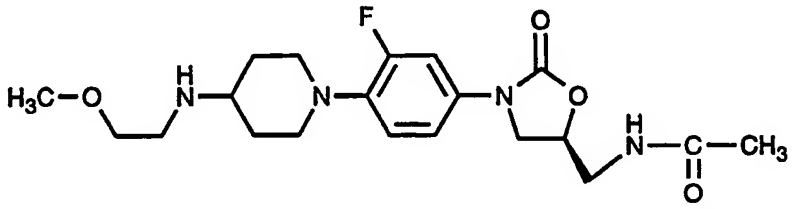
= 5.7 Hz), 4.68 - 4.75 (2H, m), 7.06 - 7.19 (2H, m), 7.49 (1H, dd, J = 1.9, 14.6 Hz), 8.23 (1H, t, J = 5.8 Hz).

Compound No. 67



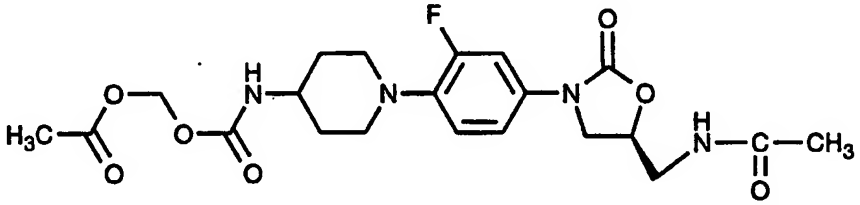
^{1}H NMR (DMSO-d_6) δ ppm: 1.54 - 1.60 (2H, m), 1.83 (3H, s), 1.80 - 2.00 (2H, m), 2.73 (2H, m), 3.16 - 3.34 (3H, m), 3.40 (2H, t, J = 5.4 Hz), 3.70 (1H, dd, J = 6.2, 9.2 Hz), 4.08 (1H, t, J = 9.2 Hz), 4.70 (1H, m), 7.07 (1H, t, J = 9.5 Hz), 7.16 (1H, dd, J = 2.4, 9.5 Hz), 7.47 (1H, dd, J = 2.4, 14.6 Hz), 7.97 (1H, d, J = 9.7 Hz), 8.11 (1H, d, J = 9.7 Hz), 8.23 (1H, t, J = 5.9 Hz).

Compound No. 68



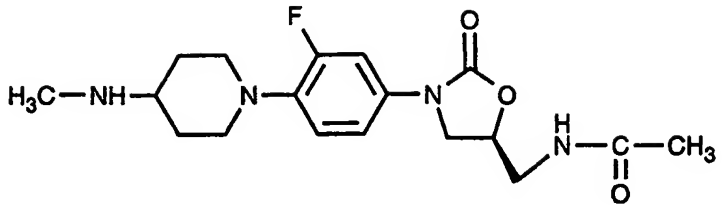
^{1}H NMR (DMSO-d_6) δ ppm: 1.32 - 1.43 (2H, m), 1.83 (3H, s), 1.86 - 1.90 (2H, m), 2.46 - 2.54 (1H, m), 2.62 - 2.70 (2H, m), 3.23 - 3.42 (6H, m), 3.33 (3H, s), 3.69 (1H, dd, J = 6.3, 9.3 Hz), 4.07 (1H, dd, J = 8.9, 8.9 Hz), 4.65 - 4.74 (1H, m), 7.02 - 7.17 (2H, m), 7.45 (1H, dd, J = 2.4, 15.1 Hz), 8.23 (1H, t, J = 5.5 Hz).

Compound No. 69



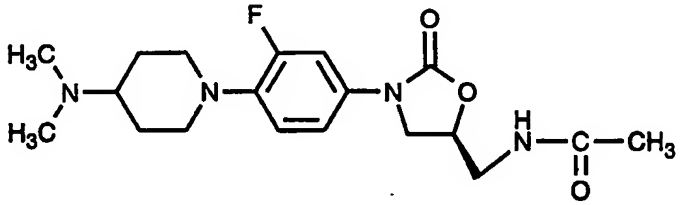
^{1}H NMR(DMSO-d_6) δ ppm: 1.51 - 1.63 (2H, m), 1.82 - 1.87 (2H, m), 1.83 (3H, s), 2.06 (3H, s), 2.66 - 2.74 (2H, m), 3.24 - 3.28 (2H, m), 3.38 - 3.50 (3H, m), 3.66 - 3.72 (1H, m), 4.07 (1H, dd, J = 9.0, 9.0 Hz), 4.65 - 4.74 (1H, m), 5.63 (2H, s), 7.03 - 7.17 (2H, m), 7.46 (1H, dd, J = 2.3, 15.0 Hz), 7.65 (1H, d, J = 7.8 Hz), 8.23 (1H, t, J = 5.7 Hz).

Compound No. 70



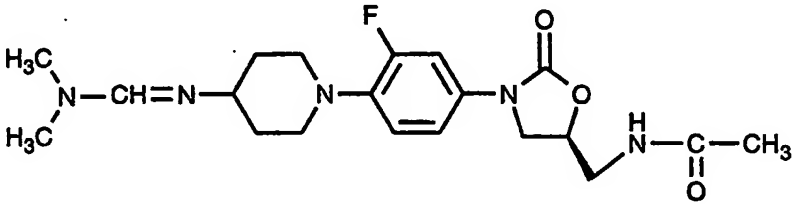
^{1}H NMR (DMSO-d_6) δ ppm: 1.31 - 1.45 (2H, m), 1.83 (3H, s), 1.84 - 1.90 (2H, m), 2.29 (3H, s), 2.31 - 2.44 (1H, m), 2.62 - 2.70 (2H, m), 3.23 - 3.28 (2H, m), 3.20 - 3.40 (1H, m), 3.38 - 3.42 (2H, m), 3.69 (1H, dd, J = 6.3, 8.8 Hz), 4.07 (1H, dd, J = 8.8, 8.8 Hz), 4.65 - 4.74 (1H, m), 7.02 - 7.17 (2H, m), 7.45 (1H, dd, J = 2.4, 15.1 Hz), 8.23 (1H, t, J = 5.9 Hz).

Compound No. 71



^{1}H NMR (DMSO-d_6) δ ppm: 1.46 - 1.59 (2H, m), 1.83 - 1.89 (2H, m), 1.88 (3H, s), 2.13 - 2.20 (1H, m), 2.19 (6H, s), 2.58 - 2.66 (2H, m), 3.28 - 3.35 (2H, m), 3.37 - 3.42 (2H, m), 3.69 (1H, dd, J = 6.3, 9.3 Hz), 4.07 (1H, dd, J = 8.8, 8.8 Hz), 4.65 - 4.74 (1H, m), 7.01 - 7.17 (2H, m), 7.45 (1H, dd, J = 2.6, 14.7 Hz), 8.22 (1H, t, J = 5.9 Hz).

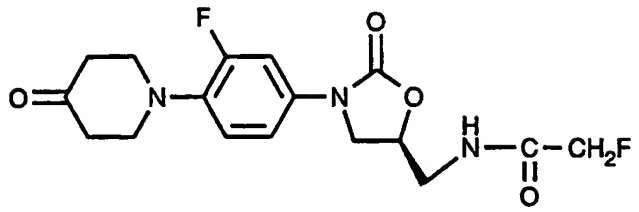
Compound No. 72



^{1}H NMR ($CDCl_3$) δ ppm: 1.74 - 1.86 (4H, m), 2.02 (3H, s), 2.71 - 2.80 (2H, m), 2.85 (6H, s), 3.05 (1H, m), 3.40 - 3.45 (2H, m), 3.60 - 3.76 (3H, m), 4.01 (1H, t, J = 9.2 Hz), 4.77 (1H, m), 6.23 (1H, br s), 6.94 (1H, t, J = 8.9 Hz), 7.05 (1H, dd, J = 2.4, 8.9

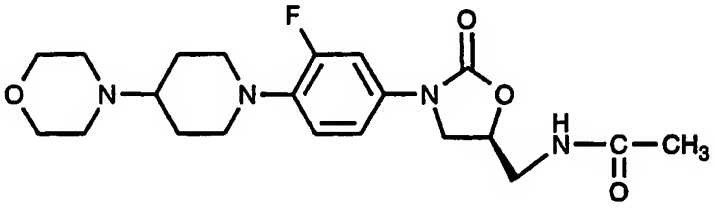
Hz), 7.37 (1H, dd, J = 2.4, 14.0 Hz), 7.38 (1H, s).

Compound No. 73



^{1}H NMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 5.7 Hz), 3.38 (4H, t, J = 5.7 Hz), 3.49 - 3.89 (3H, m), 4.07 (1H, t, J = 9.2 Hz), 4.74 (1H, d, J = 1.6 Hz), 4.80 (1H, m), 4.92 (1H, d, J = 1.6 Hz), 6.81 (1H, br s), 6.98 (1H, t, J = 9.2 Hz), 7.10 (1H, dd, J = 2.4, 9.2 Hz), 7.46 (1H, dd, J = 2.4, 14.0 Hz).

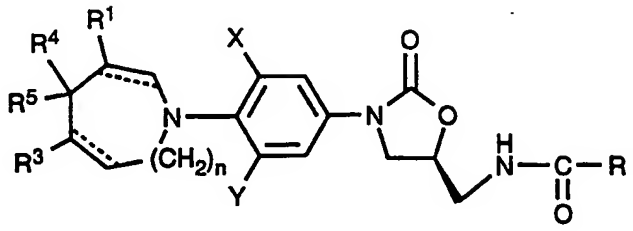
Compound No. 74



^{1}H NMR (DMSO-d_6) δ ppm: 1.54 - 1.61 (2H, m), 1.83 (3H, s), 1.80 - 2.00 (2H, m), 2.09 - 2.68 (8H, m), 3.30 (1H, m), 3.38 (2H, m), 3.50 - 3.58 (4H, m), 3.69 (1H, dd, J = 6.8, 9.2 Hz), 4.05 (1H, t, J = 9.2 Hz), 4.70 (1H, m), 7.05 (1H, t, J = 9.5 Hz), 7.14 (1H, dd, J = 2.4, 9.5 Hz), 7.45 (1H, dd, J = 2.4, 14.6 Hz), 8.23 (1H, t, J = 5.9 Hz).

CLAIMS

1. An oxazolidinone derivative represented by the general formula:



wherein

R is

(a) hydrogen atom,

(b) C_1-C_8 alkyl,

(c) C_3-C_6 cycloalkyl,

(d) amino,

(e) C_1-C_8 alkylamino,

(f) C_1-C_8 dialkylamino,

(g) C_1-C_8 alkoxy, or

(h) C_1-C_8 halogenoalkyl;

R^1 and R^3 are each and independently

(a) hydrogen atom,

(b) halogen atom,

(c) C_1-C_8 alkyl,

(d) C_3-C_6 cycloalkyl,

(e) $-(CH_2)_m-OR^{11}$, or

(f) $-C(=O)-R^{41}$;

X and Y are each and independently

(a) hydrogen atom, or

(b) halogen atom;

R^4 and R^5 are each and independently

(a) hydrogen atom,

(b) C_1-C_8 alkyl,

(c) C_1-C_8 alkoxy,

(d) C_1-C_8 alkylthio,

(e) $-(CH_2)_m-OR^{51}$,

(f) $-O-(CH_2)_m-OR^{51}$,

(g) $-NR^{42}R^{52}$,

(h) $-N=CH-NR^{44}R^{55}$,

(i) $-C(=O)-NR^{42}R^{52}$, or

(j) $-(CH_2)_m-C(=A)-R^{41}$,

or they may combine together to form

(k) =O,

(l) $=NR^{43}$,

(m) =S,

(n) $=CR^{44}R^{54}$, or

(o) an optionally substituted, unsaturated or saturated 5- or 6-membered hetero ring having 1-3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom;

R^{11} and R^{12} are each and independently

(a) hydrogen atom,

(b) C_1-C_8 alkyl, or

(c) methoxymethyl;

R^{41} is

(a) hydrogen atom,

(b) $-(CH_2)_m-OH$,

(c) C_1-C_8 alkyl,

(d) C_1-C_8 alkoxy,

(e) $-O-CH_2-O-C(=O)-R^{11}$, or

(f) $-(CH_2)_m-C(=O)-OR^{11}$;

R^{42} and R^{52} are each and independently

(a) hydrogen atom,

(b) $-(CH_2)_m-OR^{11}$,

(c) C_1-C_8 alkyl,

(d) $-C(=O)-R^{41}$,

(e) $-C(=O)-NR^{11}R^{12}$,

(f) $-(CH_2)_p$-phenyl,

(g) thiazol-2-yl,

or they may combine together to form a pyrrolidino group, a piperidino group, a piperazino group, a morpholino group, or a thiomorpholino group, each of which may be substituted by C_1-C_8 alkyl or $-(CH_2)_m-OH$;

R^{43} is

(a) hydrogen atom,

(b) $-OR^{51}$,

(c) C_1-C_8 alkyl,

(d) C_1-C_8 alkoxy,

(e) -$(CH_2)_p$-phenyl,

(f) -$NR^{42}R^{52}$,

(g) -NH-C(=NH)-NH_2,

(h) [1,2,4]triazol-4-yl, or

(i) cyano;

R^{44} and R^{54} are each and independently

(a) hydrogen atom,

(b) C_1-C_8 alkyl,

(c) -C(=O)-R^{41}, or

(d) -$(CH_2)_p$-phenyl;

R^{51} is

(a) hydrogen atom,

(b) C_1-C_8 alkyl,

(c) C_1-C_8 alkyl substituted by one or more hydroxy,

(d) C_2-C_8 alkenyl,

(e) C_1-C_8 halogenoalkyl,

(f) -$(CH_2)_m$-OR^{11},

(g) -$(CH_2)_m$-C(=O)-R^{41},

(h) -C(=O)-$(CH_2)_m$-OR^{44}, or

(i) tosyl;

A is

(a) oxygen atom, or

(b) ethyleneketal;

--- is a double bond or a simple bond;

m's are each and independently 0, 1 or 2;

n is 0 or 1;

p's are each and independently 1, 2, 3 or 4;

and C_1-C_8 alkyl, in each of the above definitions, may be each and independently substituted by one or more substituents selected from the group consisting of a halogen atom, a hydroxy group, C_1-C_8 alkoxy group, C_1-C_8 acyloxy group, an amino group, C_1-C_8 alkylamino group, C_1-C_8 dialkylamino group, -CN group and a carboxyl group,

or a pharmaceutically acceptable salt thereof.

2. The oxazolidinone derivative according to claim 1 wherein R^4 and R^5 combine

together to form

(a) =O,

(b) $=NR^{43}$

or a pharmaceutically acceptable salt thereof.

3. The oxazolidinone derivative according to claim 1, which is selected from the group consisting of:

(S)-1-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperidine-4-carboxylic acid ethyl ester,

(S)-N-[3-(3-fluoro-4-piperidin-1-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

(S)-N-{3-[3-fluoro-4-(4-hydroxy-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-{3-[3-fluoro-4-(4-hydroxymethyl-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-{3-[4-(4-dibenzylamino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-{3-[4-(4-amino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-{3-[3-fluoro-4-(4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-1-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperidine-4-carboxylic acid,

(S)-N-{3-[4-(4-acetylamino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-(1-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperidin-4-yl)-2-hydroxy-acetamide,

(S)-N-{3-[3-fluoro-4-(4-hydroxyimino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-{3-[3-fluoro-4-(4-methoxymethoxy-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-{3-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-{3-[3-fluoro-4-(4-methoxyimino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

(S)-N-{3-[3-fluoro-4-(4-methoxycarbonylamino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-{3-[3-fluoro-4-(4-methoxycarbonylhydrazono-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-(3-{3-fluoro-4-[4-(2-methyl-[1,3]dioxolan-2-ylmethyl)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

(S)-N-(3-{3-fluoro-4-[4-(2-oxo-propyl)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

(S)-8-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-1,4-dioxa-8-aza-spiro[4.5]decane-6-carboxylic acid methyl ester,

(S)-1-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-4-oxo-piperidin-3-carboxylic acid methyl ester,

(S)-N-{3-[3-fluoro-4-(4-oxo-4H-pyridin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-(3-{3-fluoro-4-[4-(2-methyl-[1,3]dioxolan-2-yl)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

(S)-N-{3-[4-(4-acetyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-{3-[3-fluoro-4-(3-hydroxymethyl-4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-{3-[3-fluoro-4-(4-methoxycarbonyloxyimino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-{3-[3-fluoro-4-(4-semicarbazono-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-(3-{3-fluoro-4-[4-(morpholin-4-ylimino)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

(S)-N-[3-(3-fluoro-4-{4-[(2-hydroxy-ethyl)-hydrazono]-piperidin-1-yl}-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

(S)-N-{3-[3-fluoro-4-(4-amidinohydrazono-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-{3-[3-fluoro-4-(4-acetoxyacetoxyimino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-(3-{3-fluoro-4-[4-(2-hydroxymethyl-[1,3]dioxolan-2-yl)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

(S)-N-{3-[3-fluoro-4-(4-benzyloxyacetoxyimino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-{3-[3-fluoro-4-(4-hydrazono-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-(1-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperidin-4-ylideneaminooxy)-acetic acid methyl ester,

(S)-N-(3-{3-fluoro-4-[4-(2-hydroxy-ethoxyimino)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

(S)-N-[3-(3-fluoro-4-{4-[4-(2-hydroxy-ethyl)-piperazin-1-ylimino]-piperidin-1-yl}-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

(S)-N-[3-(3-fluoro-4-{4-[(2-hydroxy-acetyl)-hydrazono]-piperidin-1-yl}-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

(S)-N-(3-{3-fluoro-4-[4-([1,2,4]triazol-4-ylimino)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

(S)-N-{3-[3-fluoro-4-(2-hydroxymethyl-1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-(3-{3-fluoro-4-[4-(2-methoxymethoxy-ethoxyimino)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

(S)-N-(3-{3-fluoro-4-[4-(2-hydroxy-acetyl)-1-oxa-4,8-diaza-spiro[4.5]dec-8-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

(S)-N-{3-[4-(4-cyanoimino-piperidin-1-yl)-3-fluoro-phenyl)-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-(1-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperidin-4-ylidenehydrazinocarbonyl)-acetic acid ethyl ester,

(S)-N-(3-{3-fluoro-4-[2-(methoxymethoxy-methyl)-1,4-dioxa-8-aza-spiro[4.5]dec-8-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

(S)-N-{3-[4-(4-allyloxyimino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-{3-[3-fluoro-4-(4-methoxyamino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-{3-[3-fluoro-4-(4-methoxymethoxyimino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

toluene-4-sulfonic acid (S)-1-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperidin-4-yl ester,

(S)-N-(3-{4-[4-(2,3-dihydroxy-propoxyimino)-piperidin-1-yl]-3-fluoro-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

(S)-N-(3-{3-fluoro-4-[4-(thiazol-2-ylamino)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

(S)-N-(3-{3-fluoro-4-[4-(2-methoxy-ethylamino)-piperidin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

(S)-N-(3-{4-[4-(acetoxy-methoxy-carbonylamino)-piperidin-1-yl]-3-fluoro-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide,

(S)-N-{3-[3-fluoro-4-(4-methylamino-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-{3-[4-(4-dimethylamino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-N-{3-[4-(4-dimethylaminomethyleneamino-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide,

(S)-2-fluoro-N-{3-[3-fluoro-4-(4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide and

(S)-N-{3-[3-fluoro-4-(4-morpholin-4-yl-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide

or a pharmaceutically acceptable salt thereof.

4. An antimicrobial agent comprising an oxazolidinone derivative according to claim 1 or a pharmaceutically acceptable salt thereof as an effective ingredient.

5. An antimicrobial agent comprising an oxazolidinone derivative according to claim 2 or a pharmaceutically acceptable salt thereof as an effective ingredient.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 95/02972

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D413/10 A61K31/42 C07D417/14 C07D413/14 C07D491/10 C07D498/10 //(C07D491/10,317:00,221:00),(C07D498/10,263:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,93 23384 (THE UPJOHN COMPANY) 25 November 1993 cited in the application see claims ---	1,4,5
Y	WO,A,93 09103 (THE UPJOHN COMPANY) 13 May 1993 cited in the application see claims ---	1,4,5
Y	EP,A,0 352 781 (E.I. DU PONT DE NEMOURS AND COMPANY) 31 January 1990 cited in the application see claims -----	1,4,5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 April 1995	- 9. 05. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Henry, J

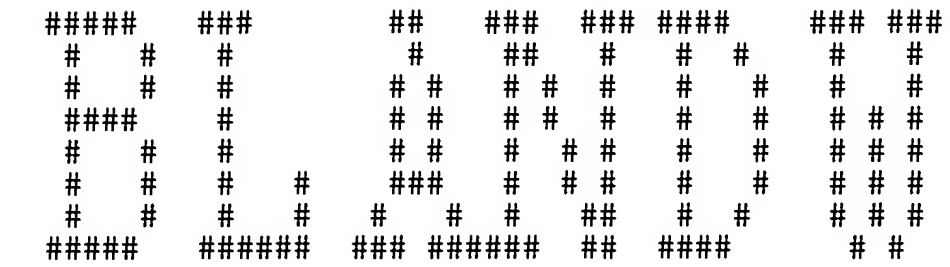
Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...information on patent family members

Inter. ...al Application No
PCT/US 95/02972

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9323384	25-11-93	AU-B-	4287793	13-12-93
		CN-A-	1079964	29-12-93
		EP-A-	0640077	01-03-95
		FI-A-	945246	08-11-94
		NO-A-	944237	04-01-95
WO-A-9309103	13-05-93	AU-A-	2689892	07-06-93
		CA-A-	2119556	13-05-93
		EP-A-	0610265	17-08-94
		JP-T-	7500603	19-01-95
EP-A-352781	31-01-90	US-A-	4948801	14-08-90
		AU-B-	622465	09-04-92
		AU-A-	3911589	01-02-90
		JP-A-	2124877	14-05-90
		US-A-	5130316	14-07-92
		US-A-	5043443	27-08-91
		US-A-	5254577	19-10-93



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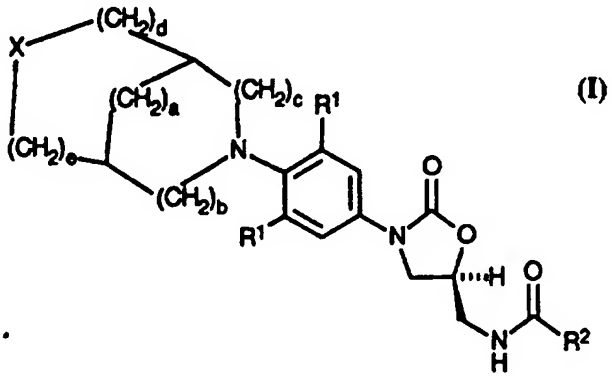
(57) Abstract

Phenyloxazolidinone compounds of formula (I) or a pharmaceutically acceptable salt thereof characterized by a bicyclic thiazine or oxazine substituent. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiply-resistant staphylococci, streptococci and enterococci as well as anaerobic organisms such as *Bacteroides spp.* and *Clostridia spp.* species, and acid-fast organisms such as *Mycobacterium tuberculosis*, *Mycobacterium avium* and *Mycobacterium spp.*



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BICYCLIC OXAZINE AND THIAZINE OXAZOLIDINONE ANTIBACTERIALS

Background of the Invention

The subject invention discloses new and useful phenyloxazolidinone compounds characterized by having either a bicyclic thiazine or oxazine substituent. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiply-resistant staphylococci, streptococci and enterococci as well as anaerobic organisms such as *Bacteroides spp.* and *Clostridia spp.* species, and acid-fast organisms such as *Mycobacterium tuberculosis*, *Mycobacterium avium* and *Mycobacterium spp.*

Information Disclosure

The present compounds are related by their phenyloxazolidinone ring structure to those disclosed in the publications below except that the subject compounds have either a bicyclic thiazine or oxazine phenyl substituent. The instant compounds have useful antibacterial activity.

PCT/US94/08904 application discloses oxazolidinone antibacterial compounds having either a morpholine or thiomorpholine substituent.

PCT/US93/03570 application discloses oxazolidinones containing a substituted diazine moiety and their uses as antimicrobials.

PCT/US92/08267 application discloses substituted aryl and heteroaryl-phenyl-oxazolidinones useful as antibacterial agents.

PCT/US89/03548 application discloses 5'indolinyl-5ß-amidomethyloxazolidinones, 3-(fused-ring substituted)phenyl-5ß-amidomethyloxazolidinones, and 3-(nitrogen substituted)phenyl-5ß-amidomethyloxazolidinones which are useful as antibacterial agents.

Other references disclosing various oxazolidinones include US Patent 4,801,600, 4,921,869, Gregory W. A., et al., J. Med. Chem., 32, 1673-81 (1989); Gregory W. A., et al., J. Med. Chem., 33, 2569-78 (1990); Wang C., et al., Tetrahedron, 45, 1323-26 (1989); and Brittelli, et al., J. Med. Chem., 35, 1156 (1992).

European Patent Publication 352,781 discloses phenyl and pyridyl substituted phenyl oxazolidinones.

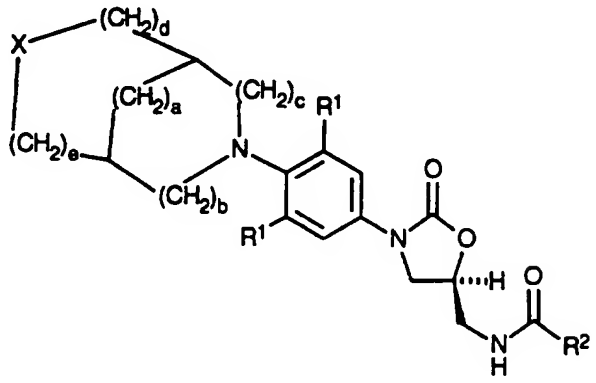
European Patent Publication 316,594 discloses 3-substituted styryl oxazolidinones.

European Patent Publication 312,000 discloses phenylmethyl and

pyridinylmethyl substituted phenyl oxazolidinones.

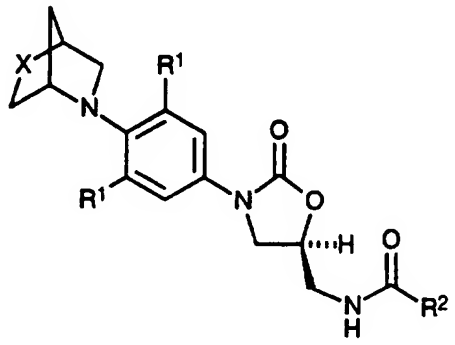
Summary of the Invention

In one aspect the subject invention is a compound of structural Formula I:



Formula I

More preferred compounds, a subset of those described by structural Formula I, are represented by structural Formula II:



Formula II

or pharmaceutically acceptable salts thereof wherein:

X is (a) O,
(b) S,
(c) SO,
(d) SO_2;

R^1 is independently H, F, Cl or OMe;

R^2 is (a) hydrogen,
(b) C_1-C_8 alkyl optionally substituted with one or more of the following: F, Cl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy,
(c) C_3-C_6 cycloalkyl,
(d) amino,
(e) C_1-C_8 alkylamino,
(f) C_1-C_8 dialkylamino,
(g) C_1-C_8 alkoxy;

a is 0 to 3;

b is 0 to 2;

c is 0 to 2 (provided b and c cannot both be 0);

d is 0 to 2; and

e is 0 to 2 (provided d and e cannot both be 0).

In another aspect, the subject invention is directed toward a method for treating microbial infections in humans or other warm-blooded animals by administering to a patient in need thereof an effective amount of a compound of Formula I or II as described above. The compound can be administered in a pharmaceutical composition either orally, parenterally or topically. Preferably the compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day, more preferably, from about 3.0 to about 50 mg/kg of body weight/day.

Detailed Description of the Invention

The present invention discloses novel substituted bicyclic oxazinyl- or thiazinylphenyloxazolidinones of structural Formula I and II as described above.

The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, particularly aerobic gram-positive bacteria, including multiply-resistant staphylococci and streptococci, as well as anaerobic organisms such as bacteroides and clostridia species, and acid-fast bacteria such as as *Mycobacterium tuberculosis* and other mycobacterial species.

"Alkyl" means carbon atom chains having the designated number of carbon atoms which can be either straight chained or branched.

"Alkoxy" means the designated number of carbon atoms attached to an oxygen forming such groups as methoxy ($-OCH_3$), ethyloxy, butyloxy, etc. and isomeric forms thereof.

"Acyloxy" means the designated number of carbon atoms to form an organic acid where the OH group has been deleted, such as acetyl, CH_3 CO-; benzoyl, C_6 H_5CO-.

Cycloalkyl" means the designated number of carbon atoms forming cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. and isomeric forms thereof.

"Amino" means an NH_2, "alkylamino" is where one of the hydrogen positions is replaced by an alkyl and "dialkylamino" is where both hydrogens are replaced by an alkyl group.

"Pharmaceutically acceptable salts" are acid addition salts which can be prepared by any of the art recognized means. Typical, acid addition salts include hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, malate, succinate, tartrate, cyclohexanesulfamates, methanesulfonates, ethanesulfonates, benxenesulfonates, toluenesulfonates, fumarates and other pharmaceutically acceptable couter ions for amines.

Preferably X is S.

The R^1 substituents are preferably both fluorine and, more preferably, fluorine and hydrogen.

The R^2 substituent is preferably hydrogen, methyl, dichloromethyl, hydroxymethyl or methoxy. More preferably R^2 is hydrogen, methoxy or methyl. It is most preferred that R^2 is methyl.

The preferred absolute configuration at C-5 of the oxazolidinone ring of compounds claimed in this invention is as represented in the structures of Formula I and II. This absolute configuration is called (*S*) under the Cahn-Ingold-Prelog nomenclature system. It is this (*S*)-enantiomer which is pharmacologically active. The racemic mixture is useful in the same way and for the same purpose as the pure (*S*)-enantiomer; the difference is that twice as much racemic material must be

used to produce the same antibacterial effect. It will be apparent to one skilled in the art that when an additional chiral center(s) is present in the bicyclic oxazine or thiazine fragment of compounds of structural Formula I and II, then diastereomers are possible. These diastereomers, in racemic and enantiomerically enriched forms, are also within the scope of the compounds of Formula I and II of the invention.

Preferred compounds of Formula I are

(*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 1);

(*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 2);

(*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-2,2-dioxo-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 3);

(*S*)-*N*-[[3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-*c*]pyrrol-5(3*H*)-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 4)

(*S*)-*N*-[[3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-*c*]pyrrol-5(3*H*)-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, S-oxide (Example 5)

(*S*)-*N*-[[3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-*c*]pyrrol-5(3*H*)-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, S,S-dioxide (Example 6)

cis-(S)-N-[[3-[3-fluoro-4-[3-oxa-7azabicyclo[3.3.0]octane-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Exmaple 7)

(*S*)-N-[[3-[3-fluoro-4-[(1*R*,4*R*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(2-thia-6-azabicyclo[3.2.0]heptan-6-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(3-thia-6-azabicyclo[3.2.0]heptan-6-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(3-thia-7-azabicyclo[3.3.1]nonan-7-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(3-thia-9-azabicyclo[3.3.1]nonan-9-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(2-thia-6-azabicyclo[3.2.1]octan-6-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(2-thia-6-azabicyclo[3.3.1]nonan-6-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(7-thia-3-azabicyclo[4.2.1]nonan-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(9-thia-3-azabicyclo[3.3.1]nonan-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(*S*)-N-[[3-[3-fluoro-4-(3-oxa-6-azabicyclo[3.2.0]heptan-6-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(*S*)-N-[[3-[3-fluoro-4-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(*S*)-N-[[3-[3-fluoro-4-(3-oxa-7-azabicyclo[3.3.1]nonan-7-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(*S*)-N-[[3-[3-fluoro-4-(3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(*S*)-N-[[3-[3-fluoro-4-(9-oxa-3-azabicyclo[3.3.1]nonan-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(*S*)-N-[[3-[3-fluoro-4-(2-oxa-5-azabicyclo[2.2.2]octan-5-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(*S*)-N-[[3-[3-fluoro-4-(2-oxa-6-azabicyclo[3.2.1]octan-6-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(*S*)-N-[[3-[3-fluoro-4-(3-oxa-7-azabicyclo[4.2.0]octan-7-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(*S*)-N-[[3-[3-fluoro-4-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(*S*)-N-[[3-[3-fluoro-4-(6-oxa-2-azabicyclo[3.2.1]octan-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(*S*)-N-[[3-[3-fluoro-4-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; and
(*S*)-N-[[3-[3-fluoro-4-[(1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

The most preferred compound is (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 2).

(*S*)-*N*-[[3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5(3*H*)-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 4)

(*S*)-*N*-[[3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5(3*H*)-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, S,S-dioxide (Example 6)

The pharmaceutical compositions of this invention may be prepared by combining the compounds of Formula I or II of this invention with a solid or liquid pharmaceutically acceptable carrier and, optionally, with pharmaceutically

acceptable adjuvants and excipients employing standard and conventional techniques. Solid form compositions include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be at least one substance which may also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Inert solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, cellulosic materials, low melting wax, cocoa butter, and the like. Liquid form compositions include solutions, suspensions and emulsions. For example, there may be provided solutions of the compounds of this invention dissolved in water and water-propylene glycol and water-polyethylene glycol systems, optionally containing suitable conventional coloring agents, flavoring agents, stabilizers and thickening agents.

Preferably, the pharmaceutical composition is provided employing conventional techniques in unit dosage form containing effective or appropriate amounts of the active component, that is, the compound of Formula I according to this invention.

The quantity of active component, that is the compound of Formula I or II according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the potency of the particular compound, the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

In therapeutic use for treating, or combatting, bacterial infections in warm-blooded animals, the compounds or pharmaceutical compositions thereof will be administered orally and/or parenterally at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which will be antibacterially effective. Generally, such antibacterially effective amount of dosage of active component will be in the range of about 0.1 to about 100, more preferably about 3.0 to about 50 mg/kg of body weight/day. It is to be understood that the dosages may vary depending upon the requirements of the patient, the severity of the bacterial infection being treated, and the particular compound being used. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also

be divided into multiple doses for administration, e.g., two to four times per day.

The compounds of Formula I or II according to this invention are administered parenterally, i.e., by injection, for example, by intravenous injection or by other parenteral routes of administration. Pharmaceutical compositions for parenteral administration will generally contain a pharmaceutically acceptable amount of the compound according to Formula I or II as a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as, for example, water-for-injection and a buffer to provide a suitably buffered isotonic solution, for example, having a pH of about 3-7. Suitable buffering agents include, for example, trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine to name but a few representative buffering agents. The compound according to Formula I generally will be dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 mg/ml to about 400 mg/ml of solution. The resulting liquid pharmaceutical composition will be administered so as to obtain the above-mentioned antibacterially effective amount of dosage.

The preferred method of preparation of oxazolidinones of Formula I and II in enantiomerically pure form is depicted in Charts I-IV..

As shown in Chart I, bicyclic oxazines and thiazines (commercially available or known in the literature), such as (1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptane (X = O) and (1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptane (X = S) of structure **1**, are reacted with a functionalized nitrobenzene **2** (Y = halogen or trifluoromethanesulfonate) in the presence of a suitable base such as *N,N*-diisopropylethylamine and in a suitable solvent such as acetonitrile, tetrahydrofuran (THF) or ethyl acetate at ambient to reflux temperature to provide the adducts **3**. When X = O, the nitro group of **3** is then reduced by catalytic hydrogenation in the presence of a suitable catalyst such as 10% palladium on carbon or W-2 Raney nickel, and in a suitable solvent such as ethyl acetate, tetrahydrofuran, aqueous tetrahydrofuran, methanol and mixtures thereof, to furnish the anilines **4**. In the case where X = S, the nitro group of **3** can be reduced by the action of sodium hydrosulfite in aqueous tetrahydrofuran at ambient temperature to 55 °C to give the anilines **4**. Alternatively, reduction of the nitro group of **3** (X = S) can be accomplished by catalytic hydrogenation in the presence of a suitable catalyst, such as platinum on sulfide carbon or W-2 Raney nickel, and in an appropriate solvent system, for example aqueous tetrahydrofuran. The latter conditions are especially useful in that the reaction mixture is simply filtered through Celite® or the like to remove the catalyst and the filtrate containing

the aniline **4** is directly used in the next step. To this end, the anilines **4** are converted to their benzyl ($R^3 = CH_2Ph$) or methyl ($R^3 = CH_3$) carbamate derivatives **5**, employing standard Schotten-Baumann conditions or other variations known to one skilled in the art. The urethanes **5** are then deprotonated with a suitable base such as *n*-butyllithium, lithium diisopropylamide, or lithium bis(trimethylsilyl)amide in a suitable solvent such as tetrahydrofuran or N,N-dimethylformamide and at a suitable temperature such as -78 to -60°C to give a lithiated intermediate which is then treated with commercially available (-)-(*R*)-glycidyl butyrate. Warming to ambient temperature then directly affords the 5-(hydroxymethyl)oxazolidinones **6** in enantiomerically enriched form. Compound **6** is then converted to the corresponding mesylate **7** (R^4 = methanesulfonyl) or aryl sulfonate **7** ($R^4 = ArSO_2$, for example *p*-toluenesulfonyl) by the action of, for example, methanesulfonyl chloride/pyridine or methanesulfonyl chloride/triethylamine/dichloromethane or *p*-toluenesufonyl chloride/pyridine.

As illustrated in Chart II, the resultant sulfonate derivative **7** is then reacted with an azide source such as sodium or potassium azide in an aprotic solvent such as *N,N*-dimethylformamide (DMF) or 1-methyl-2-pyrrolidinone, optionally in the presence of a catalyst such as 18-crown-6, at a temperature of 50-90 °C to afford the azide **8**. The azide is then reduced by hydrogenation with palladium on carbon or a platinum catalyst in an appropriate solvent such as ethyl acetate or methanol to give the corresponding amine **9**. Alternatively, and preferably in the case where X = S, the azide can be reduced by treatment with a trivalent phosphorus compound such as triphenylphosphine in a suitable solvent such as tetrahydrofuran followed by the addition of water. Alternatively, the mesylate or aryl sulfonate group of compounds **7** can be displaced with potassium phthalimide in acetonitrile at reflux temperature to give the intermediate phthalimide **10**. The phthalimide **10** is then deprotected by treatment with aqueous methyl amine in refluxing ethanol to afford the amine **9**. In yet another alternative, the mesylate **7** is reacted with ammonium hydroxide in hot isopropanol or isopropanol/tetrahydrofuran, preferably in a sealed reaction vessel, to directly give the amine **9**. The amine **9** is then acylated by reactions known to those skilled in the art to give oxazolidinones of structure **11**. For example, the amine can be reacted with an acid chloride or anhydride in a basic solvent such as pyridine at a temperature ranging from -30 to 30 °C to provide the acylated compound **11** (R^2 = optionally substituted alkyl). It will be apparent to one skilled in the art that other acyl groups within the scope of this invention can be

readily appended to the amine **9** by standard acylation techniques, for example those highlighted in March, J. "Advanced Organic Chemistry", 4th ed.; John Wiley & Sons: New York, 1992; pp 417-425, to give additional examples of **11**. The compounds of structure **11** represent examples of bicyclic oxazine- and thiazine-substituted oxazolidinone antibacterial agents of Formula II, which are the subject of this invention.

As shown in Chart III, the oxazolidinones **11**, themselves examples of antibacterial agents of Formula II, can be further elaborated to additional compounds of Formula II. Specifically, **11** (X = S) can be oxidized to the corresponding sulfoxide(s) **12** (X = SO) with sodium metaperiodate in a mixture of water and methanol. It will be apparent to one skilled in the art that both *endo*- and *exo*- sulfoxides are possible, and both isomeric forms, as well as mixtures thereof, are within the scope of this invention. In addition, compounds **11** or **12** can be oxidized to the corresponding sulfones **13** ($X = SO_2$) by treatment with 4-methylmorpholine *N*-oxide and catalytic osmium tetroxide in aqueous acetone. It will be apparent to those skilled in the art that alternative conditions for oxidizing **11** (X = S) to **12** or **13** are known, for example those highlighted in March, J. "Advanced Organic Chemistry", 4th ed.; John Wiley & Sons: New York, 1992; pp 1201-1202.

As shown in Chart IV synthesis of compounds which incorporate a thienopyrrolidine begins with reduction of the diester **14** to the diol **15** using lithium aluminum hydride as the reducing agent. Compound **15** is then converted to the bis-mesylate **16** by reaction with methanesulfonyl chloride and a trialkylamine base. Cyclization of **16** to the thienopyrrolidine **17** is carried out by reaction with sodium sulfide, and compound **17** is debenzylated to the thienopyrrole **18** by reaction with hydrogen in the presence of a suitable catalyst such as palladium on carbon. The compound of example 4 is then prepared from **18** by following the procedures outlined in Charts I and II (but substituting **18** for **1**). The compounds of Examples 5 and 6 are prepared by oxidation of the compound of Example 4, using the same procedures as shown in Chart III.

Antimicrobial activity was tested *in vivo* using a Murine Assay procedure. Groups of female mice were injected intraperitoneally with bacteria which were thawed just prior to use and suspended in brain heart infusion with 4% Brewer's yeast UC9213 (*Staphylococcus aureus*) or brain hear infusion (*Streptococcus species*). Antibiotic treatment a six dose levels per drug was administered on hour and five

hours after infection by either oral or subcutaneous routes. Survival was observed daily for six days. ED50 values based on mortality ratios were calculated using probit analysis. The subject compounds were compared against a well-known antimicrobial (Vancomycin) as a control. The data is shown in Table 1.

Table 1

***In Vivo* Activity Against *S. aureus* UC®9213**

Example No.	ED_{50} (mg/kg)	
	Example, PO	Vancomycin, SC
1	7.7	11.2
2	4.2	4.0
4	4.3	-
5	10.0	-
6	3.5	-

It will be apparent to those skilled in the art that the described synthetic procedures are merely representative in nature and that the use of alternative bicyclic oxazines and thiazines known in the patent and open literature allows for the preparation of additional examples of structural Formula I.

EXAMPLE 1: (*S*)-N-[[3-[4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1: 4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluoronitrobenzene

A mixture of commercially available (1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride (0.200 g, 1.47 mmol), dipotassium hydrogen phosphate (1.030 g, 5.90 mmol) and 3,4-difluoronitrobenzene (0.195 mL, 1.77 mmol) in dimethyl sulfoxide (6 mL) was stirred at ambient temperature under a N_2 atmosphere. TLC analysis (5% MeOH/$CHCl_3$) after 3 h revealed the starting nitrobenzene was consumed. The reaction mixture was diluted with H_2O and (60 mL) and extracted with $CHCl_3$. The combined organic extracts were washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to a yellow solid. Chromatography over silica gel (60 g), eluting with a gradient of 0-2% MeOH/$CHCl_3$, afforded, after concentration of appropriate fractions, 0.314 g (90%) of the title compound as a yellow solid with mp 106.5-108 °C and MS(EI) 238 (M^+).

Step 2: N-(carbobenzyloxy)-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluoroaniline

A solution of 4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluoronitrobenzene (0.160 g, 0.672 mmol) in 3:1 THF/H_2O (4 mL) was treated with acetic acid (0.115 mL) and then 10% palladium/carbon (0.020 g) under a N_2 stream. The atmosphere was replaced with H_2 (balloon) by repeated evacuation and filling and the mixture stirred at ambient temperature. After 2 h, TLC analysis (6% $CH_3CN/CHCl_3$) revealed the reduction to be complete. The reaction mixture was filtered through Celite® and the filtrate immediately placed under an atmosphere of N_2 and treated with K_2CO_3 (0.464 g, 3.36 mmol) followed by benzyl chloroformate (0.117 mL, 0.864 mmol). TLC analysis (6% $CH_3CN/CHCl_3$) after 0.5 h revealed the reaction to be complete. The reaction mixture was concentrated under reduced pressure and chromatographed over silica gel (20 g), eluting with a gradient of 1-5% $CH_3CN/CHCl_3$. Concentration of appropriate fractions afforded 0.226 g (98 %) of the title compound as a white solid with mp 120-121 °C and MS(EI) 342 (M^+).

Step 3: (*R*)-[3-[4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methanol

A solution of N-(carbobenzyloxy)-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluoroaniline (0.169 g, 0.494 mmol) in dry THF (2 mL) was cooled to -78 °C under a N_2 atmosphere and then treated with *n*-butyllithium (0.312 mL of a 1.6 M

solution in hexane, 0.499 mmol). After stirring 10 min at -78 °C, the reaction mixture was treated with (*R*)-glycidyl butyrate (0.070 mL, 0.499 mmol). When the addition was completed, the cooling bath was removed and the mixture allowed to stir at ambient temperature overnight, during which time an off-white precipitate appeared. TLC analysis (5% MeOH/$CHCL_3$) revealed the reaction to be complete. The reaction mixture was treated with ca. 5 drops of saturated aqueous NH_4Cl, which made the reaction mixture a homogeneous solution. The reaction mixture was concentrated under reduced pressure to an off-white solid. Chromatography over silica gel, eluting with a gradient of 1-5% MeOH/$CHCl_3$, afforded, after concentration of appropriate fractions, 0.116 g (84%) of the title compound as a white solid with mp 138-140 °C and MS(EI) 308 (M^+). In addition, 0.018 g (10%) of a second component, identified as the butyrate ester of the title compound by ^1H NMR analysis, was obtained as an amber oil.

Step 4: (*R*)-[[3-[4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]methanesulfonate

A solution of (*R*)-[3-[4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methanol (0.765 g, 2.48 mmol) in dry CH_2Cl_2 (30 mL) was cooled to 0 °C under a N_2 atmosphere and treated with Et_3N (0.518 mL, 3.73 mmol) followed by methanesulfonyl chloride (0.202 mL, 2.61 mmol). TLC analysis (5% MeOH/$CHCl_3$) after 0.5 h revealed the reaction to be complete. The reaction mixture was washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give 0.992 g (ca. 100%) of the title compound as a tan solid. An analytical sample was prepared by recrystallization from 5% CH_2Cl_2/*i*-PrOH. This sample had mp 124.5-126 °C and MS(EI) 386 (M^+).

Step 5: (*R*)-[[3-[4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]azide

A solution of (*R*)-[[3-[4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]methanesulfonate (0.869 g, 2.25 mmol) in dry DMF (10 mL) was tretaed with solid NaN_3 (0.732 g, 11.3 mmol) at ambient temperature under N_2. The mixture was then heated to 65 °C and reaction progress monitored by TLC. After 7.5 h at this temperature, TLC analysis (5% MeOH/$CHCl_3$) revealed the reaction to complete. The reaction mixture was diluted with EtOAc (100 mL), washed with H_2O (3 x 15 mL) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 0.692 g (92%) of the title

compound as a tan solid. An analytical sample was prepared by recrystallization from 1:1 EtOAc/hexane as an off-white solid with mp 101-102.5 °C and MS(EI) 333 (M^+).

Step 6: (*S*)-N-[[3-[4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A solution of (*R*)-[[3-[4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]azide (0.652 g, 1.96 mmol) in MeOH (20 mL) and CH_2Cl_2 (10 mL) was treated with 10% palladium/carbon (0.095 g) under a N_2 stream. The atmosphere was then replaced with H_2 (balloon) by repeated evacuation and filling and the mixture stirred at ambient temperature under H_2. After 3 h, TLC analysis (5% MeOH/$CHCl_3$) revealed the reduction to be complete. The reaction mixture was filtered through Celite® and the filtrate concentrated under reduced pressure. The crude 5-(aminomethyl)oxazolidinone was dissolved in CH_2Cl_2 (20 mL) and treated with pyridine (0.190 mL, 2.35 mmol) and then acetic anhydride (0.222 mL, 2.35 mmol). After 0.5 h, TLC analysis (5% MeOH/$CHCl_3$) indicated the acetylation to be complete. The reaction mixture was washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give an off-white solid. Chromatography over silica gel (70 g), eluting with a gradient of 1-3% MeOH/$CHCl_3$, afforded, after concentration of appropriate fractions, 0.517 g (76%) of the title oxazolidinone antibacterial agent as a white solid with mp 60-65 °C and MS(EI) 349 (M^+).

EXAMPLE 2: (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1: 4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluoronitrobenzene

A mixture of commercially available (1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptane (0.500 g, 3.30 mmol), diisopropylethylamine (1.434 mL, 8.24 mmol) and 3,4-difluoronitrobenzene (0.437 mL, 3.96 mmol) in dry acetonitrile (15 mL) was heated to reflux temperature under a N_2 atmosphere for 1 h and then cooled to ambient temperature overnight. The reaction mixture was concentrated under reduced pressure to give a yellow syrup. Chromatography over silica gel (50 g), eluting with chloroform, afforded, after concentration of appropriate fractions, 0.700 g (84%) of the title compound as a yellow solid with mp 97-98 °C and MS(EI) 254 (M^+).

Step 2: N-(carbobenzyloxy)-4-[(1S,4S)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluoroaniline

A solution of 4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluoronitrobenzene (1.64 g, 6.46 mmol) in 20% H_2O/THF (50 mL) was treated with platinum on sulfide carbon (0.200 g) under a N_2 stream. The atmosphere was replaced with H_2 (balloon) by repeated evacuation and filling. After 12 h TLC analysis revealed a significant amount of starting material still remained. The reaction mixture was transferred to a Parr apparatus and shaken under 45 psi H_2. TLC analysis after 2 h indicated some starting material still remained. The reaction mixture was filtered through Celite® and the filtrate, containing a mixture of the desired aniline intermediate and starting nitrobenzene derivative, was cooled to 0 °C and treated with $NaHCO_3$ (2.170 g, 25.8 mmol) and benzyl chloroformate (1.02 mL, 7.10 mmol). After 0.5 h the reaction mixture was concentrated under reduced pressure to a yellow/green syrup. This material was dissolved in $CHCl_3$, washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Filtration through a plug of silica gel, eluting with 20-30% EtOAc/hexane, afforded, after concentration of appropriate fractions, a mixture of starting nitrobenzene derivative and the title compound. This material taken-up in 20% H_2O/THF (50 mL) and treated with W-2 Raney nickel (ca. 0.400 g). The reaction mixture was shaken on a Parr apparatus under 45 psi H_2. After 3 h the reaction mixture was filtered through Celite® and the filtrate cooled to 0 °C and treated with $NaHCO_3$ (2.00 g, 23.8 mmol) followed by benzyl chloroformate (0.600 mL, 4.19 mmol). After 0.5 h the reaction mixture was concentrated under reduced pressure and the residue chromatographed over silica gel (125 g), eluting with 10-20% EtOAc/hexane, to afford, after concentration of appropriate fractions, 2.20 g (95%) of the title compound as a yellow solid mp 91-93 °C and MS(EI) 358 (M^+).

Step 3: (*R*)-[3-[4-[(1S,4S)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methanol

A solution of N-(carbobenzyloxy)-4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluoroaniline (0.359 g, 1.00 mmol) in dry THF (4 mL) under N_2 was cooled to -78 °C and then treated with *n*-butyllithium (0.633 mL of a 1.6 M solution in hexane, 1.01 mmol). The reaction mixture was stirred at -78 °C for 15 min and then treated with (*R*)-glycidyl butyrate (0.151 mL, 1.00 mmol). When the addition was complete, the cooling bath was removed and the reaction mixture allowed to warm to ambient temperature overnight. TLC analysis (5% MeOH/$CHCl_3$) indicated the reaction was

complete but a small amount of the butyrate ester of the title compound was present. The addition of 5 drops of a 25 wt.% solution of NaOMe/MeOH, followed by stirring for 20 min at room temperature, was effective in converting this intermediate to the title compound. The reaction mixture was treated with saturated aqueous NH_4Cl (10 drops) and then concentrated under reduced pressure to an oil. This material was dissolved in CH_2Cl_2 and washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a crude product. Chromatography over silica gel (50 g), eluting with 1-3% MeOH/$CHCl_3$, afforded, after concentration of appropriate fractions, 0.132 g (41%) of the title compound as an oil. Trituration with EtOAc afforded a precipitate, which was isolated and dried *in vacuo* to give an off-white solid with mp 156-157 °C and MS(EI) 324 (M^+).

Step 4: (*R*)-[[3-[4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]methanesulfonate

A solution of (*R*)-[3-[4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methanol (1.68 g, 5.19 mmol) in dry CH_2Cl_2 (100 mL) under N_2 was cooled to 0 °C and treated with Et_3N (0.793 mL, 5.70 mmol) followed by methanesulfonyl chloride (0.442 mL, 5.70 mmol). After 0.5 h at this temperature, the reaction appeared to be complete by TLC analysis (5% MeOH/$CHCl_3$). The mixture was washed with H_2O, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give 1.65 g (79%) of the title compound as a white solid with mp 139-142 °C and MS(EI) 402 (M^+).

Step 5: (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A mixture of (*R*)-[[3-[4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]methanesulfonate (1.56 g, 3.88 mmol), 1:1 THF/*i*-PrOH (4 mL) and 30% NH_4OH (4 mL) was heated to 95 °C in a sealed tube for 14 h and then cooled to ambient temperature. TLC analysis (5% MeOH/$CHCl_3$) revealed the reaction to be complete. The mixture was diluted with CH_2Cl_2 (75 mL), washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a syrup. The crude 5-(aminomethyl)oxazolidinone intermediate was dissolved in CH_2Cl_2 (75 mL) and treated with pyridine (0.345 mL, 4.27 mmol) and acetic anhydride (0.403 mL, 4.27 mmol) at ambient temperature. After 1 h, TLC analysis (5% MeOH/$CHCl_3$)

indicated the acetylation to be complete. The reaction mixture was washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to an amber solid. Chromatography over silica gel (125 g), eluting with 1-3% MeOH/$CHCl_3$, afforded, after concentration of appropriate fractions, 1.23 g (87%) of the title oxazolidinone antibacterial agent as a solid with mp 90-95 °C and MS(EI) 365 (M^+).

EXAMPLE 3: (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-2,2-dioxo-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A solution of (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (0.300 g, 0.82 mmol) in 25% H_2O/acetone (16 mL) was treated at ambient temperature with 4-methylmorpholine-N-oxide (0.288 g, 2.47 mmol) followed by osmium tetroxide (0.102 mL of a 2.5 wt.% solution in *tert*-butanol, 0.008 mmol). After 18 h, TLC analysis (10% MeOH/$CHCl_3$) revealed the oxidation was complete. The reaction mixture was treated with saturated aqueous $NaHSO_3$ and then extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed over silica gel (10 g), eluting with 1-3% MeOH/$CHCl_3$, to afford, after concentration of appropriate fractions, 0.321 g (98%) of the title oxazolidinone antibacterial agent as a white solid with mp 95-105 °C.

EXAMPLE 4: (*S*)-*N*-[[3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5(3*H*)-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1: *cis*-1-(Phenylmethyl)-3,4-pyrrolidinedimethanol

(*cis*)-1-(Phenylmethyl)-3,4-pyrrolidinedicarboxylic acid, dimethyl ester was prepared according to the procedure of Y. Terao, et al (*Chem. Pharm. Bull.*, **1985**, *33*, 2762-66). To a stirred solution of this diester (12.14 g, 43.8 mmol) in dry THF (175 mL) under N_2 cooled to 0 °C was added dropwise a solution of lithium aluminum hydride (1M in THF, 87 mL, 87 mmol) over 15 min. The reaction mixture was stirred at 0 °C for 1 h, then at RT for 18 h. The reaction mixture was cooled to 0 °C and quenched with successive addition of H_2O (3.2 mL), 5 N NaOH (3.2 mL) and H_2O (11.7 mL). The reaction mixture became very thick and stirring was difficult. The reaction mixture was diluted with ether (500 mL) and filtered through a small pad of celite. The filter cake was washed with ether (250 mL). The filtrate was washed

with H_2O (1 x 300 mL) and the organics were dried ($MgSO_4$), filtered and concentrated to afford 9.3 g (41.8 mmol, 96%) of the desired diol and a thick yellow oil. Used without further purification. HRMS (FAB) calcd for $C_{13}H_{19}NO_2$+H 222.1494, found 222.1490.

Step 2: *cis*-1-(Phenylmethyl)-3,4-di(methylsulfonyloxy)methylpyrrolidine

To a stirred solution of *cis*-1-(phenylmethyl)-3,4-pyrrolidinedimethanol (9.2 g, 41.6 mmol) in CH_2Cl_2 (240 mL) cooled to 0 °C was added triethylamine (29 mL, 208.1 mmol) followed by methanesulfonyl chloride (8.1 mL, 104.0 mmol). The reaction mixture was stirred at 0 °C for 15 min, then at RT for 1.5 h. The reaction mixture was poured into H_2O (240 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (1 x 100 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography using ethyl acetate as the eluent to afford 14.2 g (37.5 mmol, 90%) of the desired bis-mesylate as a thick yellow oil. HRMS (EI) calcd for $C_{15}H_{23}NO_6S_2$ 377.0967, found 377.0958.

Step 3: Hexahydro-5-(phenylmethyl)-1*H*-thieno[3,4-c]pyrrole

To a stirred solution of *cis*-1-(phenylmethyl)-3,4-di(methylsulfonyloxy)methylpyrrolidine (9.2 g, mmol), in dry DMSO (48 mL) was added anhydrous sodium sulfide (5.7 g, 73.3 mmol). The dark reaction mixture was heated at 120 °C for 18 h. The cooled reaction mixture was poured into ice H_2O (150 mL). The resulting mixture was extracted with ether (3 x 200mL). The combined organics were dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by flash chromatography using ethyl acetate as the eluent to afford 4.2 g (19.1 mmol, 78%) of the desired product as a thick yellow oil. HRMS (EI) calcd for $C_{13}H_{17}NS$ 219.1082, found 219.1080. Anal. Calcd for $C_{13}H_{17}NS$: C, 71.19; H, 7.81; N, 6.39. Found: C, 70.82; H, 7.83; N, 6.35.

Step 4: Hexahydro-1*H*-thieno[3,4-c]pyrrole, hydrochloride

To a stirred solution of hexahydro-5-(phenylmethyl)-1*H*-thieno[3,4-c]pyrrole (1.2 g, 5.3 mmol) in CH_2Cl_2 (21 mL) cooled to 0 °C was added dropwise *via* syringe 1-chloroethylchloroformate (1.15 mL, 10.7 mmol). The reaction mixture was stirred at 0 °C for 20 min, then at RT for 90 min. The reaction mixture was concentrated. The resulting residue was purified by flash chromatography using 25 % ethyl acetate in hexane as the eluent to afford 611.3 mg (2.6 mmol, 49%) of 1-

chloroethylcarbamate. The column was then washed with 20% methanolic ammonia in $CHCl_3$ to afford 160.5 mg (1.24 mmol, 23 %) of desired amine as the free base. The 1-chloroethylcarbamate (611.3 mg, 2.6 mmol) was dissolved in methanol (15 mL) and heated at reflux for 90 min. The cooled reaction mixture was concentrated to afford 408.0 mg (2.5 mmol, 47%) of the desired amine as the HCl salt (based on chlorocarbamte). mp 149-151 °C; HRMS (EI) calcd for $C_6H_{11}NS$ 129.0612, found 129.0614. Anal. Calcd for $C_6H_{12}ClNS$: C, 43.50; H, 7.30; N, 8.45; Cl: 21.39; S: 19.35. Found: C, 43.39; H, 7.23; N, 8.24; Cl: 21.08; S: 19.12.

Step 5: 5-(2-Fluoro-4-nitrophenyl)-hexahydro-1*H*-thieno[3.4-c]pyrrole

To a stirred suspension of hexahydro-5-1*H*-thieno[3,4-c]pyrrole, hydrochloride (147.3 mg, 0.89 mmol) in acetonitrile (5 mL) was added 3,4-fluoronitrobenzene (0.11 mL, 0.98 mmol) followed by diisopropylethyl amine (0.36 mL, 2.05 mmol). The homogeneous reaction mixture was heated at reflux for 18 h. The cooled reaction mixture was concentrated. The resulting residue was diluted with EtOAc (50 mL) and washed with saturated aqueous NH_4Cl (1 x 25 mL). The aqueous layer was extracted with EtOAc (1 x 30 mL). Combined organics were washed with saturated $NaHCO_3$ (1 x 40 mL), brine (1 x 40 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography using 20 % EtOAc in hexane as the eluent to afford 202.5 mg (0.75 mmol, 89%) of the desired nitro compound as a bright yellow solid. mp 107-109 °C; Anal. calcd for $C_{12}H_{13}FN_2O_2S$: C, 53.72; H, 4.88; N, 10.44; S: 11.95. Found: C, 53.38; H, 5.03; N, 10.34; S: 11.89.

Step 6: 3-[3-Fluoro-4-(tetrahydro-1*H*-thieno[3.4-c]pyrrol-5(3*H*)-yl)phenylcarbamic acid, phenylmethylester

To a stirred suspension of 5-(2-fluoro-4-nitrophenyl)-hexahydro-1*H*-thieno[3,4-c]pyrrole (1.44 g, 5.4 mmol) in ethanol (70 mL) was added 2 M aqueous $CuSO_4$ (2.9 mL). This mixture was cooled to 0 °C and sodium borohydride (1.10 g, 26.8 mmol) was added portionwise. (Caution: Very exothermic!) The dark reaction mixture was then heated at reflux for 2 h. The cooled reaction mixture was partitioned between EtOAc and H_2O. The phases were separated. The aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated. The resulting dark residue was dissolved in acetone/H_2O (2:1, 60 mL). This stirred solution was cooled to 0 °C and solid $NaHCO_3$ (1.35 g, 16.1 mmol) was added followed by benzylchloroformate (1.9 mL, 13.4 mmol). The reaction mixture was stirred at 0 °C for 15 min, then at RT for 2 h. The reaction

mixture was quenched by careful addition of 10 % aqueous $NaHSO_4$ (30 mL). The reaction mixture was poured into EtOAc (250 mL) and the phases were separated. The aqueous layer was extracted with EtOAc (1 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography using 20% EtOAc in hexane to afford 1.6 g (4.3 mmol, 81 %) of the desired carbamate: mp 101-102 °C; Anal. Calcd for $C_{20}H_{21}FN_2O_2S$: C, 64.50; H, 5.68; N, 7.52; S: 8.61. Found: C, 64.33; H, 5.56; N, 7.53; S: 8.61.

Step 7: (5*R*)-3-[3-Fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5(3*H*)-yl)phenyl]-5-(hydroxymethyl)-2-oxazolidinone

To stirred solution of 3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5(3*H*)-yl)phenylcarbamic acid, phenylmethyl ester (1.36 g, 3.6 mmol) dry THF (14 mL) under N_2 cooled to -78 °C was added n-butylithium (1.6 M in hexane, 2.4 mL, 3.8 mmol). The reaction mixture was stirred at -78 °C for 35 min and then *R*-(-)-glycidylbutyrate (0.54 mL, 3.8 mmol) was added. The reaction mixture was stirred at -78 °C for 30 min, then at RT overnight. A thick precipitate had formed. The reaction mixture was quenched with saturated aqueous NH_4Cl (14 mL) and poured into EtOAc (50 mL). The phases were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (1 x 30 mL), brine (1 x 30 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography using EtOAc as the eluent to afford 801.6 mg (2.4 mmol, 65%) of the desired product. mp 165-167 °C; Anal. Calcd for $C_{16}H_{19}FN_2O_3S$: C, 56.79; H, 5.66; N, 8.28; S: 9.48. Found: C, 56.88; H, 5.74; N, 8.21; S: 9.33.

Step 8: (5*R*)-3-[3-Fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5(3*H*)-yl)phenyl]-5-[[(methylsulfonyl)oxy]methyl]-2-oxazolidinone

To a stirred solution of (5*R*)-3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5(3*H*)-yl)phenyl]-5-(hydroxymethyl)-2-oxazolidinone (656.5 mg, 1.9 mmol) in CH_2Cl_2 (20 mL) cooled to 0 °C was added triethylamine (0.41 mL, 2.9 mmol) followed by methanesulfonylchloride (0.18 mL, 2.3 mmol). The reaction mixture was stirred at 0 °C for 15 min, then at RT for 18 h. The reaction mixture was poured into H_2O (20 mL). the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (1 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. the residue was triturated with ether/hexane and solid was isolated by filtration and dried to afford 773.9 mg (1.9 mmol, 96%) of the desired mesylate. mp 148-150 °C; Anal. Calcd for $C_{17}H_{21}FN_2O_5S_2$: C, 49.03; H, 5.08; N, 6.73; S:

15.40. Found: C, 48.56; H, 5.12; N, 6.48; S: 15.41. Found: C, 48.46; H, 5.25; N, 6.38.

Step 9: (*S*)-*N*-[[3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5(3*H*)-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A stirred suspension of (5*R*)-3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5-(3*H*)-yl)phenyl]-5-[[(methylsulfonyl)oxy]methyl]-2-oxazolidinone (208.5 mg, 0.5 mmol) in THF (3 mL) and methanolic ammonia (3 mL) was heated in a sealed tube at 100 °C for 48 h. (The reaction mixture became homogenous at about 80 °C.) The cooled reaction mixture was concentrated and the resulting residue was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. To this stirred suspension was added pyridine (0.12 mL, 1.5 mmol) followed by acetic anhydride (60 µL, 0.6 mmol). The homogeneous reaction mixture was stirred at 0 °C for 15 min, then at RT for 1 h then concentrated. The residue was purified by flash chromatography using 7 % methanol in EtOAc as the eluent to afford 148.2 mg (0.4 mmol, 78%) of the desired acetamide. mp 143-144 °C; KF-H_2O: 0.52% Anal. Calcd for $C_{18}H_{22}FN_3O_3S$ plus 0.52% H_2O: C, 56.68; H, 5.87; N, 11.01; S: 8.40. Found: C, 56.31; H, 5.90; N, 10.74; S: 8.30.

EXAMPLE 5: (*S*)-*N*-[[3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5(3*H*)-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, S-oxide

To a stirred solution of (S)-N-[[3-[3-fluoro-4-(tetrahydro-1H-thieno[3,4-c]pyrrol-5(3H)-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide (216.8 mg, 0.57 mmol) in methanol (4 mL) and H_2O (4 mL) cooled to 0 °C was added sodium metaperiodate (134.4 mg, 0.63 mmol). The reaction mixture was stirred at 0 °C for 1 h, then at RT for 18 h. The solid precipitation was removed by filtration. The solid was washed with $CHCl_3$ (50 mL). The filtrate was washed with H_2O (1 x 30 mL). The aqueous layer was extracted with $CHCl_3$ (2 x 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography using 7% methanol in CH_2Cl_2 as the eluent to afford 195.7 mg (0.5 mmol, 87 %) of the desired sulfoxide. mp 162-164 °C; HRMS (EI) calcd for $C_{18}H_{22}FN_3O_4S$ 395.1315, found 395.1309. KF-H_2O: 2.87 % Anal. Calcd for $C_{18}H_{22}FN_3O_4S$ plus 2.87 % H_2O: C, 53.09; H, 5.76; N, 10.32; S: 7.87. Found: C, 53.07; H, 6.01; N, 10.20; S: 7.87.

EXAMPLE 6: (*S*)-*N*-[[3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5(3*H*)-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, S,S-dioxide

To a stirred solution of (S)-N-[[3-[3-fluoro-4-(tetrahydro-1H-thieno[3,4-c]pyrrol-5(3H)-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide (213.9 mg, 0.56 mmol) in 25 % acetone/H_2O (8 mL) was added N-methylmorpholine-N-oxide (198.1 mg, 1.7 mmol) followed by osmium tetroxide in *tert*-butanol (2.5 % by wt.) (30 μL, 0.08 mmol). The reaction mixture was stirred at RT for 18 h. The reaction mixture was quenched by careful addition of saturated sodium bisulfite (8 mL). The mixture was poured into CH_2Cl_2 (50 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with brine (1 x 30 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography using 7 % methanol in $CHCl_3$ as the eluent to afford 194.3 mg (0.47 mmol, 84 %) of desired sulfone. mp 135-137 °C; HRMS (EI) calcd for $C_{18}H_{22}FN_3O_5S$ 411.1264, found 411.1263. KF-H_2O: 1.10 %. Anal. Calcd for $C_{18}H_{22}FN_3O_5S$ plus 1.10 % H_2O: C, 51.96; H, 5.45 N, 10.10; S: 7.71. Found: C, 51.73; H, 5.62; N, 9.96; S: 7.75.

EXAMPLE 7: cis-(S)-N-[[3-[3-fluoro-4-[3-oxa-7azabicyclo[3.3.0]octane-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 2 and making noncritical variations but substituting hexahydro-1H-furo(3,4-c)pyrrole (Miller, A.D. *U.S. Patent 3,975,532* **1976**). (2.33 g, 20.66 mmol) for (1S, 4S)-2-thia-5-azabicyclo[2.2.1]heptane, the title compound is obtained, mp 124-126°C.

Chart I

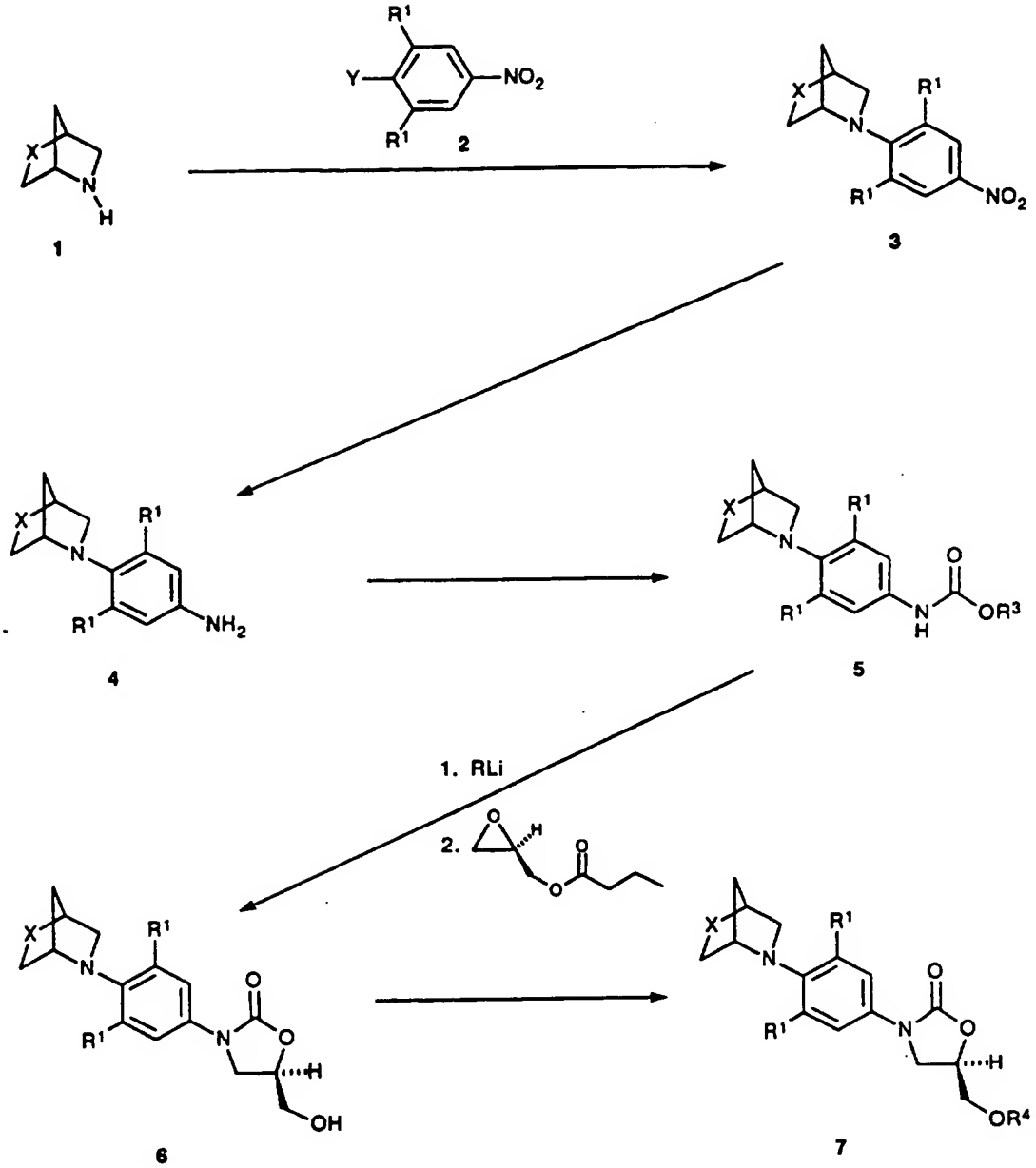
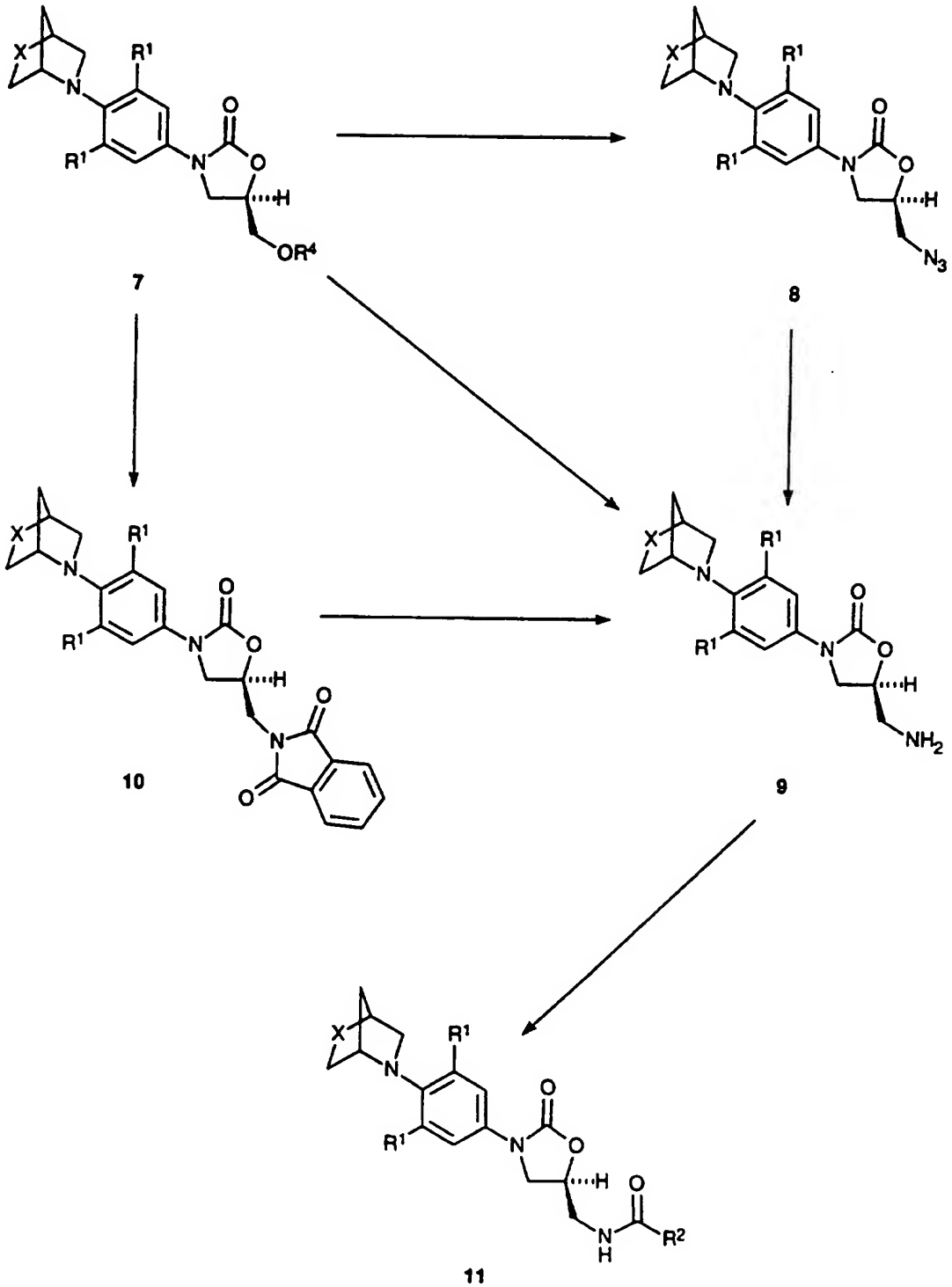


Chart II



7 8 10 9 11

Chart III

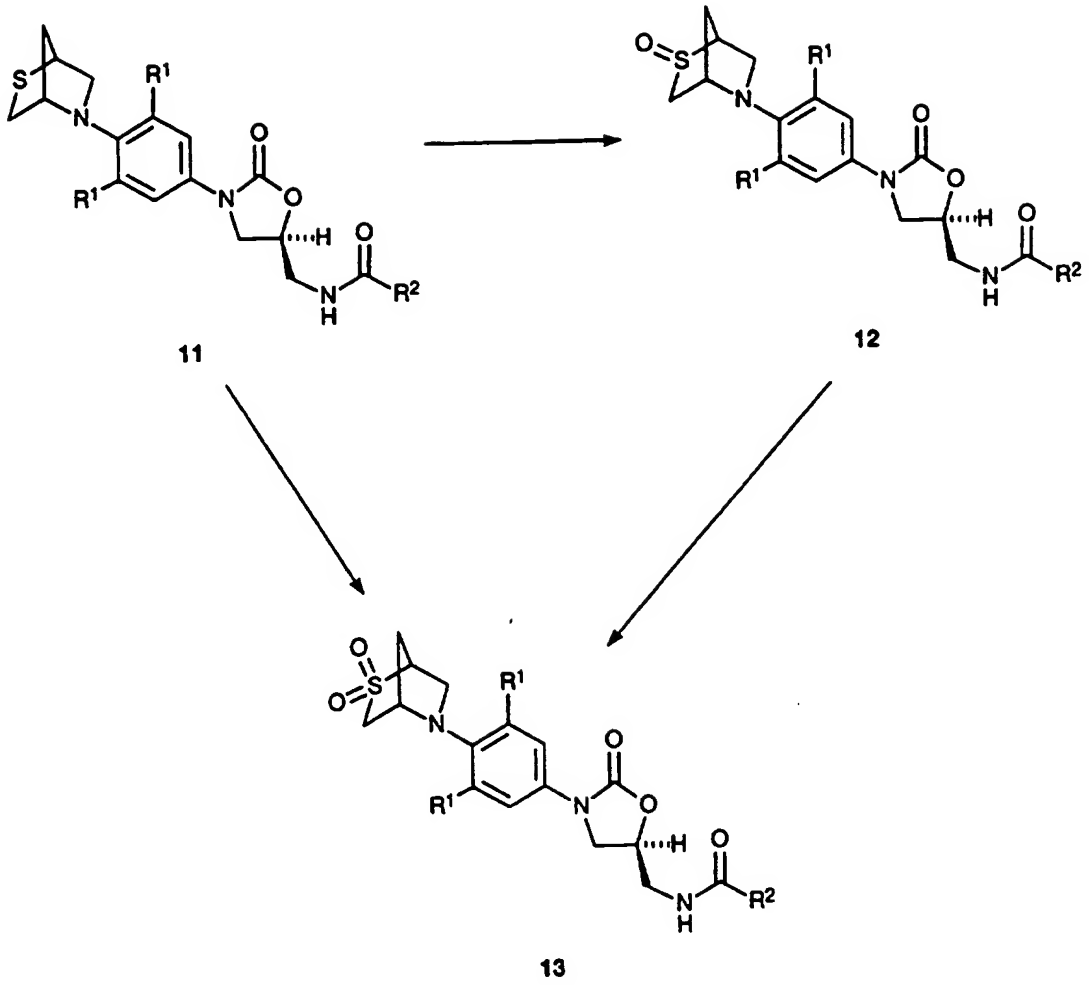
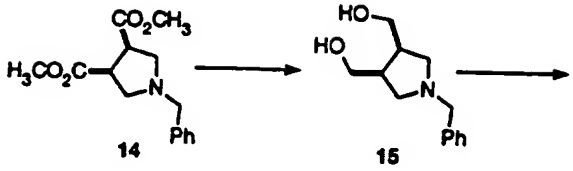
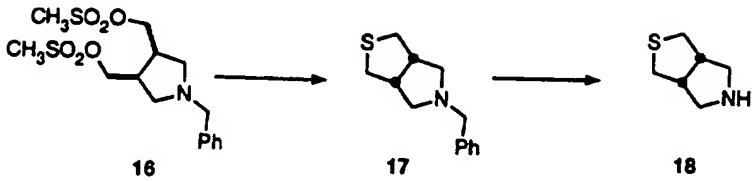


CHART IV



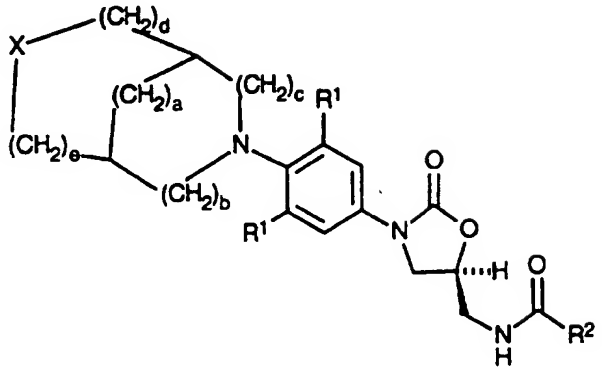
14 15



16 17 18

What is Claimed:

1. A compound of structural Formula I:



Formula I

or a pharmaceutically acceptable salt thereof wherein:

X is (a) O,
(b) S,
(c) SO,
(d) SO_2;

R^1 is independently H, F, Cl or OMe;

R^2 is (a) hydrogen,
(b) C_1-C_8 alkyl optionally substituted with one or more of the following: F, Cl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy,
(c) C_3-C_6 cycloalkyl,
(d) amino,
(e) C_1-C_8 alkylamino,
(f) C_1-C_8 dialkylamino,
(g) C_1-C_8 alkoxy;

a is 0 to 3; b is 0 to 2; c is 0 to 2 (provided b and c cannot both be 0); d is 0 to 2; and e is 0 to 2 (provided d and e cannot both be 0).

2. The compound of Claim 1 wherein X is S.

3. The compound of Claim 1 wherein each R^1 is independently H or F.

4. The compound of Claim 3 wherein each R^1 is F.

5. The compound of Claim 1 wherein R^2 is hydrogen, a C_1-C_8 alkoxy, or a C_1-C_8 alkyl optionally substituted with one or more Cl or OH.

6. The compound of Claim 1 wherein R^2 is methyl, dichloromethyl, hydroxymethyl, or methoxy.

7. The compound of Claim 1 which is:

a) (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

b) (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; or

c) (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-2,2-dioxo-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

8. The compound of Claim 1 which is the S-enantiomer form.

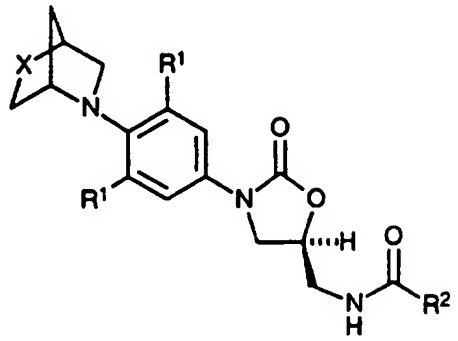
9. The compound of Claim 1 wherein c and b are both 1.

10. The compound of Claim 9 wherein d and e are both 1.

11. The compound of Claim 10 wherein a is 0.

12. The use of a compound of Formula I to prepare a medicament useful in treating microbial infections in a patient in need thereof by administering an effective amount of a compound of Formula I.

13. A compound of structural Formula II:



Formula II

or pharmaceutically acceptable salts thereof wherein:

X.is (a) O,

(b) S,

(c) SO,

(d) SO_2;

R^1 is independently H, F, Cl or OMe; and

R^2 is (a) hydrogen,

(b) C_1-C_8 alkyl optionally substituted with one or more of the following: F, Cl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy,

(c) C_3-C_6 cycloalkyl,

(d) amino,

(e) C_1-C_8 alkylamino,

(f) C_1-C_8 dialkylamino,

(g) C_1-C_8 alkoxy.

14. The compound of Claim 13 which is the S-enantiomer form.

15. The use of a compound of Formula II to prepare a medicament useful in treating microbial infections in warm-blooded animals by administering to a patient in need thereof an effective amount of a compound of Formula II.

INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/US 95/12751

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D491/048 C07D491/08 C07D495/04 C07D495/08 A61K31/42
//(C07D491/048,307:00,209:00),(C07D491/08,307:00,209:00),
(C07D495/04,333:00,209:00),(C07D495/08,333:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than mimmum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,93 23384 (UPJOHN) 25 November 1993 see claims 1,11 ---	1,12,13, 15
A	JOURNAL OF MEDICINAL CHEMISTRY., vol.33, no.9, 1990, WASHINGTON US pages 2569 - 2578 W. A. GREGORY ET AL 'Antibacterials. Synthesis and structure-activity studies of 3-aryl-2-oxooxazolidines. 2. The "A" group' cited in the application see table VI ---	1,12,13, 15
P,X	WO,A,95 07271 (UPJOHN) 16 March 1995 cited in the application see claims 1,15 --- -/--	1,12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 February 1996	14.02.1996

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Voyiazoglou, D

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/12751

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO,A,95 14684 (UPJOHN) 1 June 1995 see claims 1,9	1,12,13, 15

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter..onal Application No
PCT/US 95/12751

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		CN-A-	1079964	29-12-93
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		EP-A-	0640077	01-03-95
		FI-A-	945246	08-11-94
		JP-T-	7506829	27-07-95
		NO-A-	944237	04-01-95
		SK-A-	133794	07-06-95
WO-A-9507271	16-03-95	AU-B-	7557094	27-03-95
WO-A-9514684	01-06-95	AU-B-	8010394	13-06-95